

**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

SEBELA INTERNATIONAL LIMITED,  
SEBELA IRELAND LIMITED, and  
SEBELA PHARMACEUTICALS INC.,

Plaintiffs,

vs.

ACTAVIS LABORATORIES FL, INC.,  
ACTAVIS PHARMA, INC., TEVA  
PHARMACEUTICALS USA, INC., and  
TEVA PHARMACEUTICAL  
INDUSTRIES LTD.,

Defendants.

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SEBELA INTERNATIONAL LIMITED,  
SEBELA IRELAND LIMITED, and  
SEBELA PHARMACEUTICALS INC.,

Plaintiffs,

vs.

PRINSTON PHARMACEUTICAL INC.,  
SOLCO HEALTHCARE U.S. LLC. and  
HUAHAI U.S. INC.,

Defendants.

Case No. 2:17-cv-04789-CCC-MF

**Motion Date: July 28, 2017**

Case No. 2:17-cv-04964-CCC-MF

**DECLARATION OF ANDREW S. MCELLIGOTT IN SUPPORT OF DEFENDANTS'  
OPPOSITION TO PLAINTIFFS' MOTION FOR TEMPORARY RESTRAINING  
ORDER AND PRELIMINARY INJUNCTION**

Pursuant to 28 U.S.C. § 1746, I, Andrew S. McElligott, declare as follows:

1. I am an attorney at the law firm of Brinks Gilson & Lione, and am counsel for Defendants Actavis Laboratories FL, Inc., Actavis Pharma, Inc., Teva Pharmaceuticals USA, Inc., and Teva Pharmaceutical Industries, Ltd. (collectively, “Actavis”) in this action.

2. A true and correct copy of the file history U.S. Patent Application No. 14/577,227, which was filed on December 19, 2014, and issued as U.S. Patent No. 9,393,237, is attached hereto as Exhibit 34 and numbered '237 FH -0001-256.

3. A true and correct copy of a letter from the U.S. Food and Drug Administration to Actavis regarding approval of ANDA 207139, which was digitally signed by Heidi Lee on June 20, 2017, is attached hereto as Exhibit 35 and numbered ACTBRIS0102318-22.

4. A true and correct copy of an email from Actavis’s paralegal, Alissa Askuvich, to counsel from Sebela dated June 22, 2017, to which Actavis’s production numbered ACTBRIS0102318-22 was attached, is attached hereto as Exhibit 36.

5. A true and correct copy of a Joint Stipulation, dated November 2, 2016, and entered as Docket No. 171 in *In re Sebela Patent Litigation*, No. 14-cv-6414, is attached hereto as Exhibit 37.

6. A true and correct copy of a webpage entitled “Eight-Week Efficacy & Safety Study of Brisdelle™ (Formerly Known as Mesafem) in the Treatment of Vasomotor Symptoms Associated with Menopause,” which was access on July 19, 2017 and is available at <https://clinicaltrials.gov/ct2/show/NCT00786188?id=NCT00786188&rank=1>, is attached hereto as Exhibit 38.

7. A true and correct copy of excerpts of the trial transcript in *In re Sebela Patent Litigation*, Case No. 14-cv-6414 are attached hereto as Exhibit 39.

8. A true and correct copy of excerpts of the file history U.S. Patent Application No. 12/292,960, which was filed December 1, 2008, and issued as U.S. Patent No. 8,658,663, is attached hereto as Exhibit 40. These excerpts include:

- Brief on Appeal dated August 4, 2011 and numbered NOV-BRIS-0167178-167250; and
- Record of Oral Hearing Held October 15, 2013 numbered NOV-BRIS-0167493-167504.

9. A true and correct copy of U.S. Patent Application Publication No. 2004/0067254, dated April 8, 2004, is attached hereto as Exhibit 41 and numbered ACTBRIS0013643-13653.

10. A true and correct copy of Alan S. Nies et al., *Principles of Therapeutics*, in Goodman & Gilman's The Pharmacological Basis of Therapeutics 43 (Alfred Goodman Gilman et al. eds., 9th ed. 1996), is attached hereto as Exhibit 42 and numbered ACTBRIS0014019-14048.

11. A true and correct copy of Martin S. Lipsky et al., *From Idea to Market: The Drug Approval Process*, 14 J. Am. Board Fam. Med. 362 (2001), is attached hereto as Exhibit 43 and numbered ACTBRIS0013654-13659.

12. A true and correct copy of Asset Purchase Agreement between Noven and Sebela dated July 25, 2016 is attached hereto as Exhibit 44 and marked as PTX 463. (Highly Confidential – filed under seal)

13. A true and correct copy of excerpts from Deposition of Snehal Shah dated April 20, 2016 is attached hereto as Exhibit 45. (Highly Confidential – filed under seal)

14. A true and correct copy of Charles L. Loprinzi et al., *Pilot Evaluation of Venlafaxine Hydrochloride for the Therapy of Hot Flashes in Cancer Survivors*, 16 J. Clinical Oncology 2377 (1998) is attached hereto as Exhibit 46 and numbered ACTBRIS0013660-13664.

A handwritten signature in black ink, appearing to read "Andrew McElligott", written over a horizontal line.

Andrew S. McElligott

Dated: July 20, 2017

# EXHIBIT 34

Atty. Dkt. No. 091856-0158

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

First Inventor Name: Patricia Allison Tewes RICHARDS

Title: Method of Treating Thermoregulatory  
Dysfunction with Paroxetine

Prior Appl. No.: 14/157,992

Prior Appl. Filing  
Date: 1/17/2014

Examiner: Unassigned

Art Unit: Unassigned

**CONTINUING PATENT APPLICATION**  
**TRANSMITTAL LETTER**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Commissioner:

Transmitted herewith for filing under 37 C.F.R. § 1.53(b) is a:

[ **X** ] Continuation [ ] Division [ ] Continuation-In-Part (CIP)

of the above-identified copending prior application in which no patenting, abandonment, or termination of proceedings has occurred. Priority to the above-identified prior application is hereby claimed under 35 U.S.C. § 120 for this continuing application. The entire disclosure of the above-identified prior application is considered as being part of the disclosure of the accompanying continuing application and is hereby incorporated by reference therein.

Atty. Dkt. No. 091856-0158

Enclosed are:

[ X ] Application Data Sheet (37 CFR 1.76).

[ X ] Description, Claim(s), and Abstract (15 pages).

The adjustment to the number of sheets for EFS-Web filing follows:

Number of Sheets		EFS-Web Adjustment	Number of Sheets for EFS-Web
15	x	75%	12

The filing fee is calculated below at the large entity rate:

	Number Filed	Included in Basic Fee	Extra		Rate	Fee Totals
Basic Filing Fee					\$280.00 =	\$280.00
Search Fee					\$600.00	\$600.00
Examination Fee					\$720.00	\$720.00
Size Fee	12	- 100	= 0	x	\$400.00	\$0.00
Total	12	- 20	= 0	x	\$80.00 =	\$0.00
Claims:						
Independents	1	- 3	= 0	x	\$420.00 =	\$0.00
:						
If any Multiple Dependent Claim(s) present:				+	\$780.00 =	\$0.00
Surcharge under 37 CFR 1.16(e) for late filing of Executed Declaration and late payment of filing fee				+	\$140.00 =	\$140.00
Prioritized Examination fee (Track I) under 37 C.F.R. § 1.17 (c)						\$0.00
Processing Fee (Track I) under 37 C.F.R. § 1.17 (i)						\$0.00
TOTAL FILING FEE:					=	\$1740.00

The required filing fees are not enclosed but will be submitted in response to the Notice to File Missing Parts of Application.

Atty. Dkt. No. 091856-0158

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date December 19, 2014

By Courtenay C. Brinckerhoff

FOLEY & LARDNER LLP  
Customer Number: 22428  
Telephone: (202) 295-4094  
Facsimile: (202) 672-5399

Courtenay C. Brinckerhoff  
Attorney for Applicant  
Registration No. 37,288

<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	091856-0158
		Application Number	
Title of Invention	Method of Treating Thermoregulatory Dysfunction with Paroxetine		
<p>The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.</p> <p>This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.</p>			

**Secrecy Order 37 CFR 5.2**

<input type="checkbox"/>	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
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**Inventor Information:**

Inventor 1					Remove	
Legal Name						
Prefix	Given Name	Middle Name	Family Name	Suffix		
	Patricia	Allison Tewes	RICHARDS			
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service						
City	Scarsdale	State/Province	NY	Country of Residence	US	
Mailing Address of Inventor:						
Address 1		148 Edgemont Road				
Address 2						
City	Scarsdale	State/Province	NY			
Postal Code	10583	Country	US			
All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button.						
Add						

**Correspondence Information:**

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).			
<input type="checkbox"/> An Address is being provided for the correspondence information of this application.			
Customer Number	22428		
Email Address	IPDocketing@foley.com	Add Email	Remove Email

**Application Information:**

Title of the Invention	Method of Treating Thermoregulatory Dysfunction with Paroxetine		
Attorney Docket Number	091856-0158	Small Entity Status Claimed	<input type="checkbox"/>
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	0	Suggested Figure for Publication (if any)	n/a
<b>Filing By Reference :</b>			

<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	091856-0158
		Application Number	
Title of Invention	Method of Treating Thermoregulatory Dysfunction with Paroxetine		

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

### Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

### Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	<input checked="" type="radio"/> Customer Number	<input type="radio"/> US Patent Practitioner	<input type="radio"/> Limited Recognition (37 CFR 11.9)
Customer Number	22428		

### Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the application number blank.

Prior Application Status		<a href="#">Remove</a>	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
This Application	Continuation of	14/157992	2014-01-17
Prior Application Status		<a href="#">Remove</a>	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
14/157992	Continuation of	12/292960	2008-12-01
Prior Application Status		<a href="#">Remove</a>	

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	091856-0158
		Application Number	
Title of Invention	Method of Treating Thermoregulatory Dysfunction with Paroxetine		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12/292960	Continuation of	11/499586	2006-08-04
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the <b>Add</b> button.			

**Foreign Priority Information:**

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)<sup>i</sup> the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			<a href="#">Remove</a>
Application Number	Country <sup>i</sup>	Filing Date (YYYY-MM-DD)	Access Code <sup>i</sup> (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the <b>Add</b> button.			

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications**

- ☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
- NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

**Authorization to Permit Access:**

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	091856-0158
		Application Number	
Title of Invention	Method of Treating Thermoregulatory Dysfunction with Paroxetine		

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

## Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

### Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

- ☐ Assignee
 ☐ Legal Representative under 35 U.S.C. 117
 ☐ Joint Inventor
- ☐ Person to whom the inventor is obligated to assign.
 ☐ Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☐

Prefix	Given Name	Middle Name	Family Name	Suffix

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	091856-0158
		Application Number	
Title of Invention	Method of Treating Thermoregulatory Dysfunction with Paroxetine		

**Mailing Address Information For Applicant:**

Address 1			
Address 2			
City		State/Province	
Country		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

**Assignee Information including Non-Applicant Assignee Information:**

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

**Assignee 1**

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

Organization Name	NOVEN THERAPEUTICS, LLC
-------------------	-------------------------

**Mailing Address Information For Assignee including Non-Applicant Assignee:**

Address 1		11960 Southwest 144th Street	
Address 2			
City	Miami	State/Province	FL
Country	US	Postal Code	33186
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

**Signature:**

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Signature		Date (YYYY-MM-DD)	2014/12/19
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	091856-0158		
		Application Number			
Title of Invention	Method of Treating Thermoregulatory Dysfunction with Paroxetine				
First Name	Courtenay C.	Last Name	Brinckerhoff	Registration Number	37288
Additional Signature may be generated within this form by selecting the Add button.					

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

METHOD OF TREATING  
THERMOREGULATORY DYSFUNCTION  
WITH PAROXETINE

5 CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] Not Applicable

STATEMENT REGARDING FEDERALLY SPONSORED  
RESEARCH OR DEVELOPMENT

10 [0002] Not Applicable

FIELD OF THE INVENTION

[0003] The present invention relates to a method for treating a patient suffering from a thermoregulatory dysfunction, especially hot flashes and flushes associated with  
15 hormonal changes due to naturally occurring menopause (whether male or female) or due to chemically or surgically induced menopause. The method is also applicable to treating the hot flashes, hot flushes, or night sweats associated with disease states that disrupt normal hormonal regulation of body temperature. The invention further relates to use of paroxetine or a salt thereof.

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BACKGROUND OF THE INVENTION

[0004] Hot flashes or flushes are most typically seen in women who are in the process of going through menopause, but are also seen in women who have undergone surgical or

chemically induced menopause. They are also seen (less frequently) in men who are undergoing the so-called "male menopause" or who have undergone hormonal ablative therapy. The hot flashes and flushes are connected with a disruption of the hormonal control of thermoregulatory function. In addition, disease states which disrupt the normal hormonal control over thermoregulatory function also result in such hot flashes and flushes.

[0005] In the past, the primary treatment for peri- and post- menopausal women having these thermoregulatory dysfunctions have been hormonal replacement therapy primarily because of the known substantial fluctuations in estrogen levels. However, many women, especially those having a history or at higher risk of breast cancer, are reluctant or will not accept hormone replacement therapy. More recently, serotonergic compounds (such as serotonin receptor reuptake inhibitors ) and norepinephrine type compounds (particularly norepinephrine uptake inhibitors) have been investigated to some extent for the treatment of hot flashes and flushes in both men and women. Berendsen; *Hypothesis, The role of Serotonin in hot flushes*; Maturitas 36 (2000) 155-164 discusses the role of neurotransmitters, estrogens, and the drugs sertraline and venlafaxine.

[0006] US 2006-0100263 relates to combinations of bicifadine and another drug for hot flashes. Paroxetine is one of the "other" drugs mentioned as suitable for the combination therapy. US 2006-0020015 claims the use of combinations of norepinephrine reuptake inhibitors in combination with serotonin reuptake inhibitors. The '015 application also mentions that selective serotonin reuptake inhibitors are being clinically evaluated in hot

flashes and particularly mentions that fluoxetine is mentioned in this context in WO 9944601. US 2006-0020014 and US 2004-0130987 have similar disclosures. US 2004-1052710 mentions the use of serotonergic reuptake inhibitors in combination with norepinephrine reuptake inhibitors for the treatment of vasomotor symptoms (the class to which hot flashes and flushes belong) with paroxetine being specifically mentioned as one possible serotonin reuptake inhibitor. US 2002-0042432 (now US 6,369,051) claims the combinations of estrogenic substances with a selective serotonin reuptake inhibitor (SSRI) and paroxetine is specifically mentioned as one of the potential SSRIs for use in the claimed invention.

10

[0007] In addition, sertraline (another SSRI) was found to be effective to some degree in hot flashes as a standalone therapy in Trott, et al *An Open Trial of Sertraline for Menopausal Hot Flushes: Potential Involvement of Serotonin in Vasomotor Instability*; Del. Med. Jnl, September 1997, vol. 69, No. 9, 481-482 and in Roth et al; *SERTRALINE RELIEVES HOT FLASHES SECONDARY TO MEDICAL CASTRATION AS TREATMENT OF ADVANCED PROSTATE CANCER*; Psycho-Oncology 7: 129-132 (1998). US 6,498,184 discusses the role of selective 5-HT<sub>2C</sub> (a serotonin receptor subtype) agonists for the treatment of hot flushes. US 2004-0092519 relates to use of reboxetine (a selective noradrenaline reuptake inhibitor, i.e. NARI) for treating hot flushes. Finally, Stearns et al; *A pilot trial assessing the efficacy of paroxetine hydrochloride (Paxil®) in controlling hot flashes in breast cancer survivors*; Annals of Oncology 11: 17-22, 2000 reports on studies of 10 mg and 20 mg per day dosings of paroxetine hydrochloride monotherapy in women for control of hot flushes.

20

[0008] While the above disclosures mention the use of SSRIs in combinations with other drugs for hot flushes, or paroxetine in particular in combination with other drugs, or even paroxetine as monotherapy for hot flushes, all of these references only mention dosings of paroxetine at 10 mg per day or greater, and generally in the range of 20-50 mg per day. The only exception is US 6,369,051 which mentions a broad dosage range for the SSRI component of the SSRI/estrogenic substance combination, where the SSRI dose is given as 0.1-500 mg/day; preferably 1-200 mg/day, more preferably 20-50 mg/day. However this use is in combination with estrogens. Thus, it can be generally seen that antidepressant therapeutic dosing of the SSRI is typically indicated, or the range is so broad as to effectively not give any real teaching as to a particular dose.

[0009] It is generally recognized that at typical antidepressant therapeutic dosing of SSRIs (including paroxetine) there are significant side effects that the patient may not be willing to endure. Women with menopausal hot flashes may not be willing to take antidepressant doses of antidepressant drugs both due to side effects and reluctance to take a treatment for depression. In addition, patients who have multiple other drug treatments, especially cancer therapy treatments or cancer survivors generally do not want to have other medical issues to have to deal with. A simple side effect to most patients who are willing to endure the side effect in other contexts may be overwhelming to those having to deal with multiple drug treatments from other conditions. Thus, there remains a need to obtain relief from the thermoregulatory dysfunction of hot flushes and

hot flashes as well as other vasomotor disruptions of thermal regulation while minimizing the side effects and risks associated with the therapeutic agents mentioned above.

[0010] Paroxetine is a well characterized molecule in the pharmaceutical and patent literature. Chemical processes for its manufacture are detailed in US 4,861,893; US 5 6,172,233; US 6,326,496; US 6,433,179; US 6,541,637; US 6,686,473; US 6,716,985; US 6,881,845; US 6,900,327; and US 6,956,121 to name a few. It is known to exist in various solvate and polymorphic forms include various hydrates, anhydrous forms, isopropanolates, ethanlates, etc, amorphous as well as multiple crystalline forms such as are disclosed in for example, US 4,721,723; US 5,039,803; US 5,672,612; US 5,872,132; 10 US 5,900,423; US 6,080,759; US 6,133,277; US 6,436,956; US 6,440,459; and US 6,638,948, among others. Various pharmaceutical dosage forms are known from the foregoing patents as well as from US 5,955,475; US 6,113,944; US 6,645,523; US 6,660,298; and US 6,699,882 and others for example. Some paroxetine derivatives are 15 disclosed in US 6,063,927. US 6,440,459 and US 2004/0143120 disclose paroxetine maleate and making paroxetine hydrochloride from the maleate. US 2002/0193406; US 2002/0035130; and US 2001/0023253 disclose particularly the mesylate salt, but also many others. US 2002/0090394 discloses controlled release compositions of paroxetine. Paroxetine has also been indicated for a wide range of treatments ranging from its use as 20 an antidepressant (US 4,007,196) to neurologic and mental disorders, (US 5,470,846) to CNS disorders (US 5,985,322) to treatments for nicotine withdrawal, premenstrual symptoms, post-traumatic stress disorder, heroin addiction, etc. Each of the foregoing patent disclosures is incorporated herein (in its entirety) by reference.

### OBJECT OF THE INVENTION

[0011] It is therefore an object of the invention to provide to a patient suffering from a thermoregulatory dysfunction a dosage form of paroxetine suitable for administration of  
5 from 0.1 mg/day to less than an antidepressant effective dosage of paroxetine per day.

[0012] Another object of the invention is to provide to a patient suffering from a thermoregulatory dysfunction a dosage form of paroxetine suitable for administration of  
10 from 0.1 mg/day to less than 10 mg/day.

[0013] Still another object of the invention is to provide to a patient suffering from a thermoregulatory dysfunction a treatment thereof with paroxetine that substantially  
15 avoids most and/or substantially reduces the side effects typically obtained from an antidepressant effective amount of paroxetine.

[0014] Still further objects of the invention will be apparent to those of ordinary skill.

### SUMMARY OF THE INVENTION

[0015] The foregoing objects are achieved by providing a method of treating a  
20 thermoregulatory dysfunction treatment using paroxetine as free base or a pharmaceutically acceptable salt thereof, in an anhydrate, a hydrate, or solvate form, in

any non-crystalline or any crystalline polymorphic form of any of the foregoing in a dosage of from about 0.1 mg/day up to less than an antidepressant therapeutically effective amount of paroxetine.

5 BRIEF DESCRIPTION OF THE DRAWING

[0016] Not Applicable

DETAILED DESCRIPTION OF THE INVENTION

[0017] The present invention is a method of treating a thermoregulatory dysfunction  
10 treatment using paroxetine as free base or a pharmaceutically acceptable salt thereof, in an anhydrate, a hydrate, or solvate form, in any non-crystalline or any crystalline polymorphic form of any of the foregoing in a dosage of from about 0.1 mg/day up to less than an antidepressant therapeutically effective amount of paroxetine. The invention is also a dosage form of paroxetine in a dose which is less than that effective for its use as  
15 an antidepressant.

[0018] For the present invention, paroxetine may be in the form of the free base or any pharmaceutically acceptable salt thereof. Pharmaceutically acceptable salts include, but are not limited to, hydrohalides (such as hydrochloride, hydrobromide, hydroiodide),  
20 sulfates (such as sulfate, bisulfate), phosphates (such as mono, di, or tri basic phosphate), oxalate, mesylate, tosylate, pamoate, citrate, carbonate, bicarbonate, malate, fumarate, as well as many others set forth in the patent references indicated in paragraph

0010 above. Preferably, the paroxetine is present as the free base, the hydrochloride salt, or the mesylate salt or mixtures thereof. Most preferably the paroxetine is present as the hydrochloride salt or the mesylate salt. Paroxetine for use in the present invention may be in the anhydrate, hemihydrate, monohydrate, or higher hydrate forms. Paroxetine for use in the present invention may also be either amorphous or crystalline, the choice being made by the formulator depending upon the formulation and dissolution characteristics desired. Crystalline forms have better stability, but amorphous forms have faster dissolution profiles.

[0019] The dosage is about 0.1 mg/day up to less than an antidepressant effective amount of paroxetine (based on the free base, anhydrate); preferably up to about 9.5 mg/day. Preferably the paroxetine can be administered to achieve the invention in amounts of at least 0.5 mg/day, more preferably at least 1 mg/day, still more preferably at least 2 mg/day, even more preferably at least 4 mg/day, up to preferably not more than about 9 mg/day, more preferably not more than about 8.5 mg/day, still more preferably not more than 8 mg/day. Other non-limiting dosages that are specifically suitable for the present invention include 2 mg/day, 2.5 mg/day, 3 mg/day, 3.5 mg/day, 4 mg/day, 4.5 mg/day, 5 mg/day, 5.5 mg/day, 6 mg/day, 6.5 mg/day, 7 mg/day, 7.5 mg/day, 8 mg/day, and 8.5 mg/day.

[0020] The present invention is applicable to the treatment of thermoregulatory dysfunction and in particular to such conditions (without limitation) as hot flushes, hot flashes, night sweats, etc. whether or not related to menopause (female or male),

perimenopause, hormone ablative therapy (including, but not limited to, anti-estrogenic therapy and antiandrogenic therapy), treatments with other chemical agent or therapeutic agents that are antiestrogenic or antiandrogenic or interfere with thermoregulatory function, surgical procedures (such as, without limitation castration, hysterectomy, oophorectomy, etc), and disease states interfering with normal thermoregulatory functioning. Most preferably, the present invention is directed to the treatment of perimenopausal and postmenopausal hot flashes, hot flushes and night sweats in women, whether due to aging, therapeutically induced menopause, or surgically induced menopause. The invention is also preferably directed to hot flashes or hot flushes or night sweats in men whether such symptoms are due to aging, chemical castration, hormonal ablative therapy, or surgical castration.

#### Examples

[0021] The following non-limiting Examples are presented only to exemplify various embodiments of the invention and do not limit it in any fashion.

#### Example 1

[0022] Females having hot flashes associated with menopause are administered paroxetine (based on free base non-solvate, anhydrate) as follows:

Form of	Dosage	Form of	Dosage

Paroxetine		Paroxetine	
Hydrochloride	1.0	Mesylate	1.0
Hydrochloride	2.0	Mesylate	2.0
Hydrochloride	3.0	Mesylate	3.0
Hydrochloride	4.0	Mesylate	4.0
Hydrochloride	5.0	Mesylate	5.0
Hydrochloride	6.0	Mesylate	6.0
Hydrochloride	7.0	Mesylate	7.0
Hydrochloride	8.0	Mesylate	8.0
Hydrochloride	9.0	Mesylate	9.0
Hydrochloride	9.5	Mesylate	9.5

After a few days to weeks, the symptoms ameliorate.

Example 2

- 5 [0023] Females having hot flashes associated with menopause are administered paroxetine (based on free base non-solvate, anhydrate) as follows:

Form of Paroxetine HCl	Dosage	Form of Paroxetine HCl	Dosage	Form of Paroxetine HCl	Dosage
Anhydrous	1.0	Hemihydrate	1.0	Monohydrate	1.0
Anhydrous	2.0	Hemihydrate	2.0	Monohydrate	2.0

Anhydrous	3.0	Hemihydrate	3.0	Monohydrate	3.0
Anhydrous	4.0	Hemihydrate	4.0	Monohydrate	4.0
Anhydrous	5.0	Hemihydrate	5.0	Monohydrate	5.0
Anhydrous	6.0	Hemihydrate	6.0	Monohydrate	6.0
Anhydrous	7.0	Hemihydrate	7.0	Monohydrate	7.0
Anhydrous	8.0	Hemihydrate	8.0	Monohydrate	8.0
Anhydrous	9.0	Hemihydrate	9.0	Monohydrate	9.0
Anhydrous	9.5	Hemihydrate	9.5	Monohydrate	9.5

After a few days to weeks, the symptoms ameliorate.

Claims

1. A method for treating a patient suffering from a thermoregulatory dysfunction comprising administering to said patient a compound selected from paroxetine, a pharmaceutically acceptable salt thereof, a hydrate or solvate of either, in any polymorphic form, and mixtures thereof; said compound being in an amount, based on the paroxetine moiety, which is at least about 0.1 mg/day up to less than a therapeutically effective antidepressant dosage of paroxetine.
2. The method of claim 1 wherein said compound is administered in an amount of at least 0.5 mg/day.
3. The method of claim 1 wherein said compound is administered in an amount of at least 1 mg/day.
4. The method of claim 1 wherein said compound is administered in an amount of at least 2 mg/day.
5. The method of claim 1 wherein said compound is administered in an amount of at least 4 mg/day.

6. The method of claim 1 wherein said compound is administered in an amount of not more than about 9.5 mg/day.
7. The method of claim 1 wherein said compound is administered in an amount of not more than about 9 mg/day.
8. The method of claim 1 wherein said compound is administered in an amount of not more than about 8.5 mg/day.
9. The method of claim 1 wherein said compound is administered in an amount of not more than about 8 mg/day.
10. The method of claim 1 wherein said compound is administered in an amount selected from 2 mg/day, 2.5 mg/day, 3 mg/day, 3.5 mg/day, 4 mg/day, 4.5 mg/day, 5 mg/day, 5.5 mg/day, 6 mg/day, 6.5 mg/day, 7 mg/day, 7.5 mg/day, 8 mg/day, and 8.5 mg/day.
11. The method of claim 1 wherein said thermoregulatory dysfunction is the result of a condition selected from female menopausal related hormonal changes, male menopausal related hormonal changes, chemically induced hormonal changes,

surgically induced hormonal changes, hormonal disruption disease states, and any combination thereof.

12. The method of claim 1 wherein said thermoregulatory dysfunction is a condition  
5 selected from the group consisting of hot flashes, hot flushes, night sweats and combinations thereof.

METHOD OF TREATING  
THERMOREGULATORY DYSFUNCTION  
WITH PAROXETINE

5

ABSTRACT OF THE DISCLOSURE

10 The present invention relates to a method for treating a patient suffering from a thermoregulatory dysfunction, especially hot flashes and flushes associated with hormonal changes due to naturally occurring menopause (whether male or female) or due to chemically or surgically induced menopause. The method is also applicable to treating the hot flashes, hot flushes, or night sweats associated with disease states that disrupt normal hormonal regulation of body temperature.

**Electronic Acknowledgement Receipt**

<b>EFS ID:</b>	21017663
<b>Application Number:</b>	14577227
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	5836
<b>Title of Invention:</b>	METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE
<b>First Named Inventor/Applicant Name:</b>	Patricia Allison Tewes Richards
<b>Customer Number:</b>	22428
<b>Filer:</b>	Courtenay C. Brinckerhoff
<b>Filer Authorized By:</b>	
<b>Attorney Docket Number:</b>	091856-0158
<b>Receipt Date:</b>	19-DEC-2014
<b>Filing Date:</b>	
<b>Time Stamp:</b>	15:38:50
<b>Application Type:</b>	Utility under 35 USC 111(a)

**Payment information:**

Submitted with Payment	no
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**File Listing:**

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		contapp.pdf	544670 69cf9332214ecf44c50911cd239df56ca89fd26e	yes	24

Case 2:17-cv-04964-CCC-MF Document 22 Filed 07/20/17 Page 31 of 500 PageID: 1708

Multipart Description/PDF files in .zip description			
	Document Description	Start	End
	Transmittal of New Application	1	3
	Application Data Sheet	4	9
	Specification	10	20
	Claims	21	23
	Abstract	24	24
Warnings:			
Information:			
Total Files Size (in bytes):		544670	
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><b><u>New Applications Under 35 U.S.C. 111</u></b> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><b><u>National Stage of an International Application under 35 U.S.C. 371</u></b> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><b><u>New International Application Filed with the USPTO as a Receiving Office</u></b> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>			

<b>PATENT APPLICATION FEE DETERMINATION RECORD</b> Substitute for Form PTO-875				Application or Docket Number <b>14/577,227</b>		Filing Date <b>12/19/2014</b>		<input type="checkbox"/> To be Mailed	
ENTITY: <input checked="" type="checkbox"/> LARGE <input type="checkbox"/> SMALL <input type="checkbox"/> MICRO									
<b>APPLICATION AS FILED – PART I</b>									
(Column 1)			(Column 2)						
FOR		NUMBER FILED	NUMBER EXTRA		RATE (\$)		FEE (\$)		
<input checked="" type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A	N/A		N/A		<b>280</b>		
<input checked="" type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (l), or (m))		N/A	N/A		N/A		<b>600</b>		
<input checked="" type="checkbox"/> EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A	N/A		N/A		<b>720</b>		
TOTAL CLAIMS (37 CFR 1.16(i))		12 minus 20 =	* 0		x \$80 =		<b>0</b>		
INDEPENDENT CLAIMS (37 CFR 1.16(h))		1 minus 3 =	* 0		x \$420 =		<b>0</b>		
<input type="checkbox"/> APPLICATION SIZE FEE (37 CFR 1.16(s))		If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).							
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))									
* If the difference in column 1 is less than zero, enter "0" in column 2.					TOTAL		<b>1600</b>		
<b>APPLICATION AS AMENDED – PART II</b>									
(Column 1)			(Column 2)			(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =			
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =			
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))								
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
						TOTAL ADD'L FEE			
(Column 1)			(Column 2)			(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =			
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =			
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))								
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
						TOTAL ADD'L FEE			
<p>* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.</p> <p>** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".</p> <p>*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".</p> <p>The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.</p>									

LDRC  
/EVA GILLIS/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

'237 FH -0027



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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
14/577,227	12/19/2014	1629	0.00	091856-0158	12	1

CONFIRMATION NO. 5836

22428

Foley & Lardner LLP  
 3000 K STREET N.W.  
 SUITE 600  
 WASHINGTON, DC 20007-5109

## FILING RECEIPT



\*OC00000072758781\*

Date Mailed: 01/09/2015

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

## Inventor(s)

Patricia Allison Tewes Richards, Scarsdale, NY;

## Applicant(s)

Patricia Allison Tewes Richards, Scarsdale, NY;

## Assignment For Published Patent Application

Noven Therapeutics, LLC, Miami, FL

## Power of Attorney: None

## Domestic Priority data as claimed by applicant

This application is a CON of 14/157,992 01/17/2014  
 which is a CON of 12/292,960 12/01/2008 PAT 8658663  
 which is a CON of 11/499,586 08/04/2006 ABN

**Foreign Applications** for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

*Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.*

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

**If Required, Foreign Filing License Granted:** 01/08/2015

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/577,227**

**Projected Publication Date:** To Be Determined - pending completion of Missing Parts

page 1 of 3

'237 FH -0028

**Non-Publication Request:** No

**Early Publication Request:** No  
**Title**

METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE

**Preliminary Class**

514

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

## **PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES**

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

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**Title 37, Code of Federal Regulations, 5.11 & 5.15**

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<b>PATENT APPLICATION FEE DETERMINATION RECORD</b> Substitute for Form PTO-875						Application or Docket Number 14/577,227			
<b>APPLICATION AS FILED - PART I</b>									
(Column 1)		(Column 2)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY			
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)		
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280		
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600		
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720		
TOTAL CLAIMS (37 CFR 1.16(i))	12	minus 20 = *			OR	x 80 =	0.00		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1	minus 3 = *				x 420 =	0.00		
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00		
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00		
			TOTAL			TOTAL	1600		
* If the difference in column 1 is less than zero, enter "0" in column 2.									
<b>APPLICATION AS AMENDED - PART II</b>									
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY	
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)	
	Total (37 CFR 1.16(i))	*	Minus **	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus ***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))						OR		
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						OR		
			TOTAL ADD'L FEE			OR	TOTAL ADD'L FEE		
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)	
	Total (37 CFR 1.16(i))	*	Minus **	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus ***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))						OR		
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						OR		
			TOTAL ADD'L FEE			OR	TOTAL ADD'L FEE		
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.									



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/577,227	12/19/2014	Patricia Allison Tewes Richards	091856-0158

CONFIRMATION NO. 5836

## FORMALITIES LETTER



\*OC00000072758782\*

22428  
 Foley & Lardner LLP  
 3000 K STREET N.W.  
 SUITE 600  
 WASHINGTON, DC 20007-5109

Date Mailed: 01/09/2015

## NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

*Filing Date Granted***Items Required To Avoid Abandonment:**

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
- The application search fee must be submitted.
- The application examination fee must be submitted.
- Surcharge as set forth in 37 CFR 1.16(f) must be submitted.

The surcharge is due for any one of:

- late submission of the basic filing fee, search fee, or examination fee,
- late submission of inventor's oath or declaration,
- filing an application that does not contain at least one claim on filing, or
- submission of an application filed by reference to a previously filed application.

**SUMMARY OF FEES DUE:**

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. No entity status discount is in effect. If applicant is qualified for small entity status, a written assertion of small entity status must be submitted to establish small entity status. (See 37 CFR 1.27). If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- \$ 280 basic filing fee.
- \$ 140 surcharge.
- \$ 600 search fee.
- \$ 720 examination fee.
- \$( 0) previous unapplied payment amount.
- \$ 1740 TOTAL FEE BALANCE DUE.

**Items Required To Avoid Processing Delays:**

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):  
Patricia Allison Tewes Richards

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts  
Commissioner for Patents  
P.O. Box 1450  
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice".  
<https://portal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html>

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at <http://www.uspto.gov/ebc>.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/bzewdie/

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Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Atty. Dkt. No. 091856-0158

***IN THE UNITED STATES PATENT AND TRADEMARK OFFICE***

First Inventor Name: Patricia Allison Tewes RICHARDS  
Title: Method of Treating Thermoregulatory Dysfunction  
with Paroxetine  
Appl. No.: 14/577,227  
Filing Date: 12/19/2014  
Examiner: Unassigned  
Art Unit: 1629  
Confirmation Number: 5836

**PRELIMINARY AMENDMENT UNDER 37 CFR 1.115**

Mail Stop AMENDMENT  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Commissioner:

Applicant respectfully requests that the application be amended as follows prior to examination:

**Amendments to the Claims** are reflected in the listing of claims which begins on page 2.

**Remarks/Arguments** begin on page 4.

Please amend the application as follows:

**Amendments to the Claims:**

This listing of claims will replace all prior versions and listings of claims in the application:

**Listing of Claims:**

Claims 1-12 (Canceled)

13. (New) A method for treating a female patient suffering from thermoregulatory dysfunction associated with menopause, comprising administering a dosage form of paroxetine to said patient in an amount, based on the paroxetine moiety, of 7.5 mg/day.

14. (New) The method of claim 13, wherein said thermoregulatory dysfunction is a condition selected from the group consisting of hot flashes, hot flushes, night sweats, and combinations thereof.

15. (New) The method of claim 13, wherein said dosage form comprises paroxetine free base.

16. (New) The method of claim 13, wherein said dosage form comprises a pharmaceutically acceptable salt of paroxetine.

17. (New) The method of claim 13, wherein said dosage form comprises a pharmaceutically acceptable salt of paroxetine selected from the group consisting of hydrohalides, sulfates, phosphates, oxalate, tosylate, pamoate, citrate, carbonate, bicarbonate, maleate, malate, and fumarate.

18. (New) The method of claim 13, wherein said dosage form comprises a pharmaceutically acceptable salt of paroxetine selected from the group consisting of hydrochloride, hydrobromide, and hydroiodide, and combinations of two or more thereof.

Atty. Dkt. No. 091856-0158

19. (New) The method of claim 13, wherein said dosage form comprises paroxetine hydrochloride.
20. (New) The method of claim 13, wherein said dosage form comprises a pharmaceutically acceptable salt of paroxetine selected from the group consisting of sulfate and bisulfate, and combinations thereof.
21. (New) The method of claim 13, wherein said dosage form comprises paroxetine mesylate.
22. (New) The method of claim 13, wherein said dosage form comprises a pharmaceutically acceptable salt of paroxetine selected from the group consisting of mono, di, and tri basic phosphates, and combinations of two or more thereof.
23. (New) The method of claim 13, wherein said dosage form comprises paroxetine or a pharmaceutically acceptable salt thereof in anhydrate, hydrate, or solvate form, or a combination of two or more thereof.
24. (New) The method of claim 13, wherein said dosage form comprises paroxetine or a pharmaceutically acceptable salt thereof in a crystalline or amorphous form, or a combination thereof.
25. (New) The method of claim 13, wherein said dosage form comprises paroxetine or a pharmaceutically acceptable salt thereof in a crystalline form.
26. (New) The method of claim 13, wherein said dosage form comprises paroxetine or a pharmaceutically acceptable salt thereof in an amorphous form.

Atty. Dkt. No. 091856-0158

**REMARKS**

Applicant respectfully requests that the foregoing amendments be made prior to examination.

Claims 1-12 are canceled without prejudice or disclaimer. Claims 13-26 are added to recite specific embodiments supported throughout the specification as filed, including the examples, and in the original claims. The claims roughly parallel the granted claims of related patent 8,946,251, but recite a method for treating a female patient in particular. Claims 19 and 21 recite further specific embodiments discussed in paragraph [0018] and in the examples. Thus, the amendments do not introduce new matter.

Applicant respectfully awaits examination on the merits.

Should there be any questions regarding this submission, or should any issue remain, the he Examiner is invited to contact the undersigned by telephone to advance prosecution.

Respectfully submitted,

Date

August 7, 2015

By

Courtenay C. Brinckerhoff

FOLEY & LARDNER LLP

Customer Number: 22428

Telephone: (202) 295-4094

Facsimile: (202) 672-5399

Courtenay C. Brinckerhoff

Attorney for Applicant

Registration No. 37,288

Atty. Dkt. No 091856-0158

***IN THE UNITED STATES PATENT AND TRADEMARK OFFICE***

First Inventor Name: Patricia Allison Tewes RICHARDS  
Title: Method of Treating Thermoregulatory  
Dysfunction with Paroxetine  
Appl. No.: 14/577227  
Filing Date: 12/19/2014  
Examiner: Unassigned  
Art Unit: 1629  
Confirmation Number: 5836

**TRANSMITTAL OF SECOND APPLICATION DATA SHEET AND REQUEST FOR  
CORRECTED FILING RECEIPT**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Commissioner:

Attached is a Second Application Data Sheet for the captioned application.

The Second Application Data Sheet is being submitted in compliance with 37 CFR 1.76 to update the name of the Applicant to the Assignee: NOVEN THERAPEUTICS, LLC, and to update the residence and address of the inventor. These updates have been marked by strikethrough and underlining on the Second Application Data Sheet.

Applicant respectfully requests that a Corrected Filing Receipt be issued to reflect the updated Applicant and inventor information.

Atty. Dkt. No 091856-0158

Although Applicant believes no fee is due, the Commissioner is authorized to charge deposit account number 19-0741 for any required fees.

Respectfully submitted,

Date August 7, 2015

FOLEY & LARDNER LLP  
Customer Number: 22428  
Telephone: (202) 295-4094  
Facsimile: (202) 672-5399

By Courtenay C. Brinckerhoff

Courtenay C. Brinckerhoff  
Attorney for Applicant  
Registration No. 37,288

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**STATEMENT UNDER 37 CFR 3.73(c)**Applicant/Patent Owner: Patricia Allison Tewes RichardsApplication No./Patent No.: 14/577227 Filed/Issue Date: 12/19/2014Titled: Method of Treating Thermoregulatory Dysfunction with ParoxetineNOVEN THERAPEUTICS, LLC, a Corporation

(Name of Assignee)

(Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☒ The assignee of the entire right, title, and interest.
2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):
- ☐ The extent (by percentage) of its ownership interest is \_\_\_\_\_%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.
- ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (e.g., bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

- A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel \_\_\_\_\_, Frame \_\_\_\_\_, or for which a copy thereof is attached.
- B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Patricia Allison Tewes Richards To: JDS Pharmaceuticals, LLCThe document was recorded in the United States Patent and Trademark Office at  
Reel 018388, Frame 0706, or for which a copy thereof is attached.2. From: JDS Pharmaceuticals, LLC To: Noven Therapeutics, LLCThe document was recorded in the United States Patent and Trademark Office at  
Reel 020565, Frame 0921, or for which a copy thereof is attached.

[Page 1 of 2]

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

'237 FH -0040

PTO/AIA/96 (08-12)

Approved for use through 01/31/2013. OMB 0651-0031  
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**STATEMENT UNDER 37 CFR 3.73(c)**

3. From: \_\_\_\_\_ To: \_\_\_\_\_

The document was recorded in the United States Patent and Trademark Office at  
Reel \_\_\_\_\_, Frame \_\_\_\_\_, or for which a copy thereof is attached.

4. From: \_\_\_\_\_ To: \_\_\_\_\_

The document was recorded in the United States Patent and Trademark Office at  
Reel \_\_\_\_\_, Frame \_\_\_\_\_, or for which a copy thereof is attached.

5. From: \_\_\_\_\_ To: \_\_\_\_\_


The document was recorded in the United States Patent and Trademark Office at  
Reel \_\_\_\_\_, Frame \_\_\_\_\_, or for which a copy thereof is attached.

6. From: \_\_\_\_\_ To: \_\_\_\_\_

The document was recorded in the United States Patent and Trademark Office at  
Reel \_\_\_\_\_, Frame \_\_\_\_\_, or for which a copy thereof is attached.☐ Additional documents in the chain of title are listed on a supplemental sheet(s).☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.


[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

  
Signature

Courtenay C. Brinckerhoff

Printed or Typed Name

  
Date

37,288

Title or Registration Number

PTO/AIA/BO (07-12)

Approved for use through 11/30/2014, OMB 0651-0035

U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO**

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:



Practitioners associated with Customer Number:

22428

OR



Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignments documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:



The address associated with Customer Number:

22428

OR



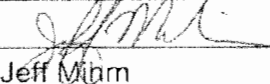
Firm or Individual Name			
Address			
City			
Country			
Telephone		Email	

Assignee Name and Address: NOVEN THERAPEUTICS, LLC  
11960 Southwest 144th Street  
Miami, Florida 33186

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

**SIGNATURE of Assignee of Record**

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date	5-16-14
Name	Jeff Minn	Telephone	(305) 253-5099
Title	Manager		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

'237 FH -0042

Atty. Dkt. No. 091856-0150

**DECLARATION**

As a below named inventor, I HEREBY DECLARE:

THAT my residence, post office address, and citizenship are as stated below next to my name;

THAT I believe I am the original, first, and sole inventor (if only one inventor is named below) or an original, first, and joint inventor (if plural inventors are named below or in an attached Declaration) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Method of Treating Thermoregulatory Dysfunction with Paroxetine

(Attorney Docket No. 091856-0150)

the application of which (check one)

       is attached hereto.

  X   was filed on 01/17/2014 as United States Application Number or PCT International Application Number 14/157,992 and was amended on        (if applicable).

THAT the above-identified application was made or authorized to be made by me.

THAT I do not know and do not believe that the same invention was ever known or used by others in the United States of America, or was patented or described in any printed publication in any country, before I (we) invented it;

THAT I do not know and do not believe that the same invention was patented or described in any printed publication in any country, or in public use or on sale in the United States of America, for more than one year prior to the filing date of this United States application;

THAT I do not know and do not believe that the same invention was first patented or made the subject of an inventor's certificate that issued in any country foreign to the United States of America before the filing date of this United States application if the foreign application was filed by me (us), or by my (our) legal representatives or assigns, more than twelve months (six months for design patents) prior to the filing date of this United States application;

THAT I have reviewed and understand the contents of the above-identified application, including the claim(s), as amended by any amendment specifically referred to above;

Atty. Dkt. No. 091856-0150

THAT I believe that the above-identified application contains a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention, and sets forth the best mode contemplated by me of carrying out the invention; and

THAT I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I HEREBY CLAIM foreign priority benefits under Title 35, United States Code §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number	Country	Foreign Filing Date	Priority Claimed?	Certified Copy Attached?

I HEREBY CLAIM the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

U.S. Provisional Application Number	Filing Date

I HEREBY CLAIM the benefit under Title 35, United States Code, §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Atty. Dkt. No. 091856-0150

U.S. Parent Application Number	PCT Parent Application Number	Parent Filing Date	Parent Patent Number
11/499,586		8/4/2006	
12/292,960		12/1/2008	

I FURTHER DECLARE THAT all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment of not more than five (5) years, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Name of first inventor	Patricia Allison Tewes RICHARDS
Residence	Bradenton, FL
Citizenship Country	US
Post Office Address	3212 Bay Drive Bradenton FL 34207
Inventor's signature	Patricia Allison Tewes Richards
Date	4/15/2017

## Electronic Patent Application Fee Transmittal

<b>Application Number:</b>	14577227			
<b>Filing Date:</b>	19-Dec-2014			
<b>Title of Invention:</b>	METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE			
<b>First Named Inventor/Applicant Name:</b>	Patricia Allison Tewes Richards			
<b>Filer:</b>	Courtenay C. Brinckerhoff			
<b>Attorney Docket Number:</b>	091856-0158			
Filed as Large Entity				
<b>Filing Fees for Utility under 35 USC 111(a)</b>				
<b>Description</b>	<b>Fee Code</b>	<b>Quantity</b>	<b>Amount</b>	<b>Sub-Total in USD(\$)</b>
<b>Basic Filing:</b>				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
<b>Pages:</b>				
<b>Claims:</b>				
<b>Miscellaneous-Filing:</b>				
Late Filing Fee for Oath or Declaration	1051	1	140	140
<b>Petition:</b>				
<b>'237 FH -0046</b>				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
<b>Patent-Appeals-and-Interference:</b>				
<b>Post-Allowance-and-Post-Issuance:</b>				
<b>Extension-of-Time:</b>				
Extension - 5 months with \$0 paid	1255	1	3000	3000
<b>Miscellaneous:</b>				
<b>Total in USD (\$)</b>				<b>4740</b>

**Electronic Acknowledgement Receipt**

<b>EFS ID:</b>	23144704
<b>Application Number:</b>	14577227
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	5836
<b>Title of Invention:</b>	METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE
<b>First Named Inventor/Applicant Name:</b>	Patricia Allison Tewes Richards
<b>Customer Number:</b>	22428
<b>Filer:</b>	Courtenay C. Brinckerhoff
<b>Filer Authorized By:</b>	
<b>Attorney Docket Number:</b>	091856-0158
<b>Receipt Date:</b>	07-AUG-2015
<b>Filing Date:</b>	19-DEC-2014
<b>Time Stamp:</b>	13:42:36
<b>Application Type:</b>	Utility under 35 USC 111(a)

**Payment information:**

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	\$4740
RAM confirmation Number	9808
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

'237 FH -0048

**File Listing:**

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		respnfmp.pdf	407134 <div>498f4cc91cfd29c916ba46586bca198507357979</div>	yes	16
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Applicant Response to Pre-Exam Formalities Notice		1	4	
	Preliminary Amendment		5	8	
	Request for Corrected Filing Receipt		9	10	
	Assignee showing of ownership per 37 CFR 3.73		11	12	
	Power of Attorney		13	13	
	Oath or Declaration filed		14	16	
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	39245 <div>b9896fde3bf54e300aefcbe366d349301fc3c02b</div>	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			446379		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Atty. Dkt. No. 091856-0158

***IN THE UNITED STATES PATENT AND TRADEMARK OFFICE***

First Inventor Name: Patricia Allison Tewes RICHARDS  
Title: Method of Treating Thermoregulatory  
Dysfunction with Paroxetine  
Appl. No.: 14/577227  
Filing Date: 12/19/2014  
Examiner: Unassigned  
Art Unit: 1629  
Confirmation Number: 5836

**TRANSMITTAL OF MISSING PARTS  
OF PATENT APPLICATION**

Mail Stop Missing Parts  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Commissioner:

In response to the Notice to File Missing Parts of Application mailed 01/09/2015, in the above-identified patent application, transmitted herewith are the missing parts to complete the filing of the subject patent application.

Enclosed are:

- ☒ Preliminary Amendment
- ☒ Transmittal of Second Application Data Sheet and Request for Corrected Filing Receipt
- ☒ Second Application Data Sheet
- ☒ Statement under 37 CFR 3.73(c)
- ☒ Power of Attorney

Atty. Dkt. No. 091856-0158

☒ Declaration☒ Information Disclosure Statement (*being filed via hand delivery*)☒ Form PTO/SB/08 and 25 references (*being filed via hand delivery*)

☒ Applicant hereby petitions for an extension of time under 37 C.F.R. §1.136(a) for the total number of months checked below:

- 
- ☐ Extension for response filed within the first month  
☐ Extension for response filed within the second month  
☐ Extension for response filed within the third month  
☐ Extension for response filed within the fourth month  
☒ Extension for response filed within the fifth month

The adjustment to the number of sheets for EFS-Web filing follows:

Number of Sheets		EFS-Web Adjustment	Number of Sheets for EFS-Web
15	x	75%	12

Atty. Dkt. No. 091856-0158

The filing fee is calculated below at the large entity rate:

	Claims as Filed		Included in Basic Fee		Extra Claims		Rate		Fee Totals
Basic Filing Fee, Search Fee & Examination Fee							\$1,600.00		\$1,600.00
Size Fee	12	-	100	=	0	x	\$400.00	=	\$0.00
Total	14	-	20	=	0	x	\$80.00	=	\$0.00
Claims:									
Independents:	1	-	3	=	0	x	\$420.00	=	\$0.00
If any Multiple Dependent Claim(s) present:						+	\$780.00	=	\$0.00
Surcharge under 37 CFR 1.16(f) for late payment of filing fee						+	\$140.00	=	\$140.00
[ X ] Extension fee for response filed within the fifth month:						+	\$3,000.00	=	\$3,000.00
Non-electronic filing fee						+		=	\$0.00
							TOTAL FILING FEE:	=	\$4,740.00
Processing Fee under 37 CFR 1.17(i) for Late Filing of English Translation of Application:						+	\$140.00	=	\$0.00
							TOTAL FEE	=	\$4,740.00
Difference to pay:						-	\$0.00	-	\$4,740.00

A credit card payment form in the amount of \$4,740.00 is enclosed in payment of the required fees.

Atty. Dkt. No. 091856-0158

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Respectfully submitted,

Date August 7, 2015

FOLEY & LARDNER LLP  
Customer Number: 22428  
Telephone: (202) 295-4094  
Facsimile: (202) 672-5399

By Courtenay C. Brinckerhoff

Courtenay C. Brinckerhoff  
Attorney for Applicant  
Registration No. 37,288

Atty. Dkt. No. 091856-0158

***IN THE UNITED STATES PATENT AND TRADEMARK OFFICE***

First Inventor Name: Patricia Allison Tewes RICHARDS  
Title: Method of Treating Thermoregulatory  
Dysfunction with Paroxetine  
Appl. No.: 14/577227  
Filing Date: 12/19/2014  
Examiner: Unassigned  
Art Unit: 1629  
Confirmation Number: 5836

**TRANSMITTAL OF MISSING PARTS  
OF PATENT APPLICATION**

Mail Stop Missing Parts  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Commissioner:

In response to the Notice to File Missing Parts of Application mailed 01/09/2015, in the above-identified patent application, transmitted herewith are the missing parts to complete the filing of the subject patent application.

Enclosed are:

- [ X ] Preliminary Amendment
- [ X ] Transmittal of Second Application Data Sheet and Request for Corrected Filing Receipt
- [ X ] Second Application Data Sheet
- [ X ] Statement under 37 CFR 3.73(c)
- [ X ] Power of Attorney

Atty. Dkt. No. 091856-0158

☒ Declaration☒ Information Disclosure Statement (*being filed via hand delivery*)☒ Form PTO/SB/08 and 25 references (*being filed via hand delivery*)

☒ Applicant hereby petitions for an extension of time under 37 C.F.R. §1.136(a) for the total number of months checked below:

- 
- ☐ Extension for response filed within the first month  
☐ Extension for response filed within the second month  
☐ Extension for response filed within the third month  
☐ Extension for response filed within the fourth month  
☒ Extension for response filed within the fifth month

The adjustment to the number of sheets for EFS-Web filing follows:

Number of Sheets	x	EFS-Web Adjustment	Number of Sheets for EFS-Web
15	x	75%	12

Atty. Dkt. No. 091856-0158

The filing fee is calculated below at the large entity rate:

	Claims as Filed		Included in Basic Fee		Extra Claims		Rate		Fee Totals
Basic Filing Fee, Search Fee & Examination Fee							\$1,600.00		\$1,600.00
Size Fee	12	-	100	=	0	x	\$400.00	=	\$0.00
Total	14	-	20	=	0	x	\$80.00	=	\$0.00
Claims:									
Independents:	1	-	3	=	0	x	\$420.00	=	\$0.00
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Surcharge under 37 CFR 1.16(f) for late payment of filing fee						+	\$140.00	=	\$140.00
[ X ] Extension fee for response filed within the fifth month:						+	\$3,000.00	=	\$3,000.00
Non-electronic filing fee						+		=	\$0.00
							TOTAL FILING FEE:	=	\$4,740.00
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Atty. Dkt. No. 091856-0158

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Respectfully submitted,

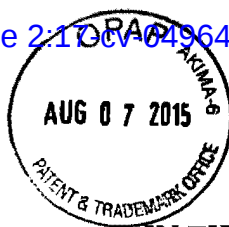
Date August 7, 2015

FOLEY & LARDNER LLP  
Customer Number: 22428  
Telephone: (202) 295-4094  
Facsimile: (202) 672-5399

By Courtenay C. Brinckerhoff

Courtenay C. Brinckerhoff  
Attorney for Applicant  
Registration No. 37,288

IFW



Atty. Dkt. No. 091856-0158

***IN THE UNITED STATES PATENT AND TRADEMARK OFFICE***

First Inventor Name: Patricia Allison Tewes RICHARDS  
Title: Method of Treating Thermoregulatory  
Dysfunction with Paroxetine  
Appl. No.: 14/577227  
Filing Date: 12/19/2014  
Examiner: Unassigned  
Art Unit: 1629  
Confirmation Number: 5836

**INFORMATION DISCLOSURE STATEMENT**  
**UNDER 37 CFR §1.56**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicant respectfully requests that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

Applicant requests that, in accordance with 37 CFR §1.98(d), the Examiner review all applications relied on for an earlier effective filing date under 35 U.S.C. 120, including Application No. 11/499,586, filed 8/4/2006; Application No. 12/292,960, filed 12/1/2008; and Application No. 14/157,992, filed 1/17/2014, for copies of references of record therein that are

Atty. Dkt. No. 091856-0158

not being provided here. Applicant would be pleased to provide copies of any such documents at the Examiner's request.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicant does not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

### **TIMING OF THE DISCLOSURE**

The listed documents are being submitted in compliance with 37 CFR §1.97(b), before the mailing date of the first Office Action on the merits.

### **RELEVANCE OF LISTED DOCUMENTS**

Documents A1-A2 are granted parent patents. Document A3 is granted sister patent filed as a continuation of Document A2. Document A4 is the published version of U.S. Application No. 11/499,586, to which this application and Documents A1-A3 claim priority.

Documents A15, A43, A49, A56-A58, A60, A64-A65, A67-A69, A85, and A87-A94, were cited by a third party as relevant to the validity of Document A2.

Documents A101 and A102 were cited during prosecution of the corresponding Japanese application. An English-language abstract is submitted for Document A101. An English-language abstract is not available for Document A102, however, Applicant provides the following concise explanation of relevance pursuant to MPEP 609.04(a):

The Japanese Office Action cited Document A102 to support the statement that  
“it was known at the effective date of the present application that the  
“thermoregulatory dysfunction” may be caused by numerous diseases such as  
neural diseases, e.g., autonomic disorder by spinal damage.”

Atty. Dkt. No. 091856-0158

Applicant therefore respectfully requests consideration of all cited references,

Although Applicant believes that no fee is required, the Commissioner is hereby authorized to charge any additional fees which may be due to Deposit Account No. 19-0741.

Respectfully submitted,

Date August 5, 2015

By Courtenay C. Brinckerhoff

FOLEY & LARDNER LLP  
Customer Number: 22428  
Telephone: (202) 295-4094  
Facsimile: (202) 672-5399

Courtenay C. Brinckerhoff  
Attorney for Applicant  
Registration No. 37,288

AUG 07 2015

PTO/SB/08 (09-06)

Approved for use through 03/31/2007. OMB 0651-0031

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO		<b>Complete if Known</b>	
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  Date Submitted: August 7, 2015  <i>(use as many sheets as necessary)</i>		Application Number	14/577,227
		Filing Date	12/19/2014
		First Named Inventor	Joel S. Lippman
		Art Unit	1629
		Examiner Name	Unassigned
Sheet 1 of 6	Attorney Docket Number	091856-0158	

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. <sup>1</sup>	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code <sup>2</sup> (if known)			
	A1	US-8,946,251	02/03/2015	RICHARDS	
	A2	US-8,658,663	02/25/2014	RICHARDS	
	A3	US-8,859,576	10/14/2014	RICHARDS	
	A4	US-2008/0033050	02/07/2008	RICHARDS	
	A5	US-4,007,196	2/8/1977	CHRISTENSEN, ET AL.	
	A6	US-4,721,723	1/26/1988	BARNES, ET AL.	
	A7	US-4,861,893	8/29/1989	BARRETT,	
	A8	US-5,039,803	8/13/1991	SMITH, ET AL.	
	A9	US-5,470,846	11/28/1995	SANDYK	
	A10	US-5,672,612	9/30/1997	ROSEN, ET AL.	
	A11	US-5,872,132	2/16/1999	WARD, ET AL.	
	A12	US-5,900,423	5/4/1999	WARD, ET AL.	
	A13	US-5,955,475	9/21/1999	KRAPE, ET AL.	
	A14	US-5,985,322	11/16/1999	ANDERSEN, ET AL.	
	A15	US-6,063,927	5/16/2000	CRAIG, ET AL.	
	A16	US-6,080,759	6/27/2000	WARD, ET AL.	
	A17	US-6,113,944	9/5/2000	PATHAK, ET AL.	
	A18	US-6,133,277	10/17/2000	WIGERNICK, ET AL.	
	A19	US-6,172,233	1/9/2001	WARD	
	A20	US-6,326,496	12/4/2001	BRENNAN	
	A21	US-6,369,051	4/9/2002	JENKINS	
	A22	US-6,433,179	8/13/2002	WANG, ET AL.	
	A23	US-6,436,956	8/20/2002	MURTHY, ET AL.	
	A24	US-6,440,459	8/27/2002	STMPA DIX DEL CORRAL, ET AL.	
	A25	US-6,498,184	12/24/2002	BERENDSEN	
	A26	US-6,541,637	4/1/2003	OKATAKE, ET AL.	
	A27	US-6,645,523	11/11/2003	LEMMENS, ET AL.	
	A28	US-6,660,298	12/9/2003	ROSEN, ET AL.	
	A29	US-6,686,473	2/3/2004	LEMMENS, ET AL.	
	A30	US-6,699,882	3/2/2004	CRAIG, ET AL.	
	A31	US-6,716,985	4/6/2004	JACEWICZ, ET AL.	
	A32	US-6,881,845	4/19/2005	FOUGET, ET AL.	
	A33	US-6,900,327	5/31/2005	BENNEKER, ET AL.	
	A34	US-6,956,121	10/18/2005	PILARSKI, ET AL.	
	A35	US-6,987,124	1/17/2006	BERENDSEN	
	A36	US-6,172,105	1/9/2001	EVENDEEN, ET AL.	
	A37	US-2006/0020015	1/26/2006	ABOU-GHARBIA, ET AL.	
	A38	US-2006/0020014	1/26/2006	ABOU-GHARBIA, ET AL.	
	A39	US-2004/0130987	7/8/2004	HUNG, ET AL.	
	A40	US-2004/0152710	8/5/2004	DEECHER, ET AL.	
	A41	US-2004/0092519	5/13/2004	HASSAN	
	A42	US-2004/0143120	7/22/2004	JACEWICZ, ET AL.	
	A43	US-2002/0193406	12/19/2002	CRAIG, ET AL.	

Examiner Signature	Date Considered
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\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP. If possible, and. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

PTO/SB/08 (09-06)

Approved for use through 03/31/2007. OMB 0651-0031

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO		<b>Complete if Known</b>	
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  Date Submitted: August 7, 2015  <i>(use as many sheets as necessary)</i>		Application Number	14/577,227
		Filing Date	12/19/2014
		First Named Inventor	Joel S. Lippman
		Art Unit	1629
		Examiner Name	Unassigned
Sheet	2	of	6
		Attorney Docket Number	091856-0158

U.S. PATENT DOCUMENTS					
Examiner	Cite No. <sup>1</sup>	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where
	A44	US-2002/0035130	3/21/2002	CRAIG, ET AL.	
	A45	US-2001/0023253	9/20/2001	CRAIG, ET AL.	
	A46	US-2002/0090394	7/11/2002	LEONARD, ET AL.	
	A47	US-2006/0100263	5/11/2006	BASILE, ET AL.	
	A48	US-2004/0086559	05/06/2004	PETERS ET AL.	
	A49	US-2004/0067254	04/08/2004	LEMMENS ET AL.	
	A50	US-2008/0254073	10/16/2008	CHI	

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS					
Examiner Initials*	Cite No. <sup>1</sup>	U.S. Patent Application Document Serial Number-Kind Code <sup>2</sup> (if known)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS					
Examiner Initials*	Cite No. <sup>1</sup>	Foreign Patent Document Country Code <sup>3</sup> Number <sup>4</sup> Kind Code <sup>5</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A51	WO 99/44601 *	9/10/1999	ELI LILLY AND COMPANY	
	A52	WO 99/47519 *	09/23/1999	SMITHKLINE BEECHAM PLC	
	A53	WO 99/56751 *	11/11/1999	ENDO PHARMACEUTICALS INC.	
	A54	WO 00/78291 *	12/28/2000	SMITHKLINE BEECHAM PLC	
	A55	WO 2007/043057 *	04/19/2007	YISSUM, RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM	
	A56	WO 02/100404 A2 ✓	12/19/2002	PANTERHEI BIOSCIENCE B.V.	
	A57	WO 2004/035058 A1 ✓	04/29/2004	WYETH	

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>6</sup>
	A58	Berendsen, "The Role of Serotonin in Hot Flushes," 36 Maturitas 155 (2000) ✓	

Examiner Signature	Date Considered
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\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP, if possible, and . The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by . This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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PTO/SB/08 (09-06)

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<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  Date Submitted: August 7, 2015  <i>(use as many sheets as necessary)</i>		Application Number	14/577,227
		Filing Date	12/19/2014
		First Named Inventor	Joel S. Lippman
		Art Unit	1629
		Examiner Name	Unassigned
Sheet 3 of 6	Attorney Docket Number	091856-0158	

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>5</sup>
	A59	CHEEMA, DEEPTI, "Non-hormonal therapy of post menopausal vasomotor symptoms: a structured evidence-based review", Arch Gynecol Obstet, Vol. 276, pp. 463-469, (2007) *	
	A60	STEARNS, MD et al.; "Paroxetine Controlled Release in the Treatment of Menopausal Hot Flashes", JAMA, Volume 289, No. 21; (June 2003) *	
	A61	ROTH, ET AL., "Sertraline Relieves Hot Flashes Secondary to Medical Castration as Treatment of Advanced Prostate Cancer," Psycho-Oncology, 7:129-132 (1998) *	
	A62	STEARNS, ET AL., "A pilot trial assessing the efficacy of paroxetine hydrochloride (Paxil) in controlling hot flashes in breast cancer survivors," Annals of Oncology; 11:17-22 (2000) *	
	A63	STEARNS, ET AL., "Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial," J. Clin Oncol, 23:6919-6930 (October 2005) *	
	A64	STEARNS ET AL., "Serotonergic Agents as an Alternative to Hormonal Therapy for the Treatment of Menopausal Vasomotor Symptoms," Treat. Endocrinol., Vol. 5, No. 2, pp. 63-67, (2006) ✓	
	A65	LOPRINZI, ET AL., "Pilot Evaluation of Paroxetine for Treating Hot Flashes in Men," Mayo Clin Proc., 79(10):1247-1251, (October 2004) *	
	A66	LOPRINZI, ET AL., "Newer antidepressants inhibit hot flashes"; Menopause, Vol. 13, No. 4, pp. 546-548 (2006) *	
	A67	Loprinzi, C.L. et al., "Pilot Evaluation of Venlafaxine Hydrochloride for the Therapy of Hot Flashes in Cancer Survivors," J. Clinical Oncology 16:2377 (1998) ✓	
	A68	Loprinzi, C.L. et al., "Venlafaxine in Management of Hot Flashes in Survivors of Breast Cancer: A Randomized Controlled Trial," Lancet 356:2059 (2000) ✓	
	A69	Trot et al., "An Open Trial of Sertraline for Menopausal Hot Flushes: Potential Involvement of Serotonin in Vasomotor Instability," Del. Med. Jr. Vol. 69, No. 9, pp. 481-482, (September 1997). ✓	
	A70	Office Action issued June 2, 2008, in U.S. Application 11/499,586, 8 pages. *	
	A71	International Search Report issued on 09/26/2008 in application number PCT/US07/17062. *	
	A72	HARADA, "Paroxetine-induced excessive yawning," Psychiatry and Clinical Neurosciences, Vol. 60, p. 260, (2006). *	
	A73	VIPPAGUNTA ET AL., "Crystalline solids," Advanced Drug Delivery Reviews, Vol. 48, pp. 3-26, (2001). *	

Examiner Signature	Date Considered
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\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP . If possible, and . The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by . This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  Date Submitted: August 7, 2015  <i>(use as many sheets as necessary)</i>		Application Number	14/577,227
		Filing Date	12/19/2014
		First Named Inventor	Joel S. Lippman
		Art Unit	1629
		Examiner Name	Unassigned
Sheet 4 of 6	Attorney Docket Number	091856-0158	

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>5</sup>
	A74	GOULD, "Salt selection for basic drugs," International Journal of Pharmaceutics, Vol. 33, pp. 210-217, (1986). *	
	A75	Office Action issued on 08/17/2010 in application number 12/292,960 (US 8,658,663) *	
	A76	Office Action issued on 12/08/2010 in application number 12/292,960 (US 8,658,663) *	
	A77	Office Action issued on 03/01/2011 in application number 12/292,960 (US 8,658,663) *	
	A78	Office Action issued on 05/31/2011 in application number 12/292,960 (US 8,658,663) *	
	A79	Notice of Allowance issued on 01/08/2014 in application number 12/292,960 (US 8,658,663) *	
	A80	Office Action issued on 08/22/2014 in application number 14/157,992 (US 8,946,251) *	
	A81	Notice of Allowance issued on 09/24/2014 in application number 14/157,992 (US 8,946,251) *	
	A82	Office Action issued on 06/27/2014 in application number 14/276,494 (US 8,859,576) ✓	
	A83	Notice of Allowance issued on 09/02/2014 in application number 14/276,494 (US 8,859,576) ✓	
	A84	European Search Report issued on 03/19/2014 in application number EP 13 19 0594. *	
	A85	LOPRINZI ET AL., "Centrally active nonhormonal hot flash therapies," The American Journal of Medicine, Vol. 118, No. 128, pp. 1185-1235, (2005). *	
	A86	CURCIO ET AL., "The Potential Role of 5-Hydroxytryptophan for Hot Flash Reduction: A Hypothesis," Alternative Medicine Review, Vol. 10, No. 3, pp. 216-221, (September 2005). ✓	
	A87	FDA approval letter for paroxetine mesylate tablets on July 3, 2003. (NDA No. 021299) *	
	A88	Fugate, S. E. et al., "Nonestrogen Treatment Modalities for Vasomotor Symptoms Associated with Menopause," Annals of Pharmacotherapy 38:1482 (2004) ✓	

Examiner Signature	Date Considered
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		First Named Inventor	Joel S. Lippman
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Sheet 5 of 6	Attorney Docket Number	091856-0158	

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	A89	Lipsky, M.S. et al., "From Idea to Market: The Drug Approval Process," J. Am. Board Fam. Med. 14:362 (2001) ✓	
	A90	Nies, A.S. et al., "Principles of Therapeutics," in Goodman & Gilman's The Pharmacological Basis of Therapeutics 43 (Alfred Goodman Gilman et al. eds.), (9th ed. 1996) ✓	
	A91	Paxil CRTM ("Paxil CR Label"), approved February 12, 2002 ✓	
	A92	Paxil CRTM ("Paxil IR Label"), approved February 12, 2002 ✓	
	A93	Pexeva® ("Pexeva Label 2003"), approved July 3, 2003 ✓	
	A94	Weitzner, M. A. et al., "A Pilot Trial of Paroxetine for the Treatment of Hot Flashes and Associated Symptoms in Women with Breast Cancer," J. Pain & Symptom Mgmt. 23:337 (2002) ✓	
	A95	NAGATA ET AL., "Short-term combinational therapy of low-dose estrogen with selective serotonin re-uptake inhibitor (fluvoxamine) for oophorectomized women with hot flashes and depressive tendencies," J. Obstet. Gynaecol. Res., Vol. 31, No. 2, pp. 107-114, (April 2005) ✓	
	A96	WISE ET AL., "Tailoring Treatment of Depression for Women Across the Reproductive Lifecycle: The Importance of Pregnancy, Vasomotor Symptoms, and Other Estrogen-Related Events in Psychopharmacology," Trends in Psychopharmacology, Vol. 13, No. 8, pp. 647-662, (August 2008). ✓	
	A97	OHKURA ET AL., "Therapeutic Effects of Estrogen Replacement Therapy (ERT), Selective Serotonin Reuptake Inhibitor (SSRI) and ERT + SSRI on Depression and Climacteric Disorder in Postmenopausal Women," Journal of Psychosomatic Obstetrics & Gynecology, Vol. 28, Supp. 1, S8-7, (December 2007), (Abstract) ✓	
	A98	KUS ET AL., "Role of estrogens in antidepressive effects of venlafaxine," European Neuropsychopharmacology, Vol. 13, Supp. 4, P.1.219, (September 2003), (Abstract) ✓	
	A99	JOE ET AL., "Estrogen Levels, Mood, Menopause-Related Symptoms and Menopausal Duration During Hormone Replacement Therapy with SSRI in Postmenopausal Women with Depression," XXIVth CINP Congress, Paris, France, P02.137, (20-24 June 2004) (Abstract) ✓	
	A100	PANDARANANDAKA ET AL., "Estrogen (E <sub>2</sub> )-Dependent Effect of the Selective Serotonin Reuptake Inhibitor (SSRI) Fluoxetine on Anxiety-Like Behaviors in Female Rats," The Journal of Physiological Sciences, Proceedings of IUPS, Vol. 60, p. 517, P5AM-9-5, (July 27-August 1, 2009) (Abstract). ✓	

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	A101	YAGUCHI ET AL., "Rehabilitation Difficulties in a Patient with a Thermoregulation Disturbance due to Striatonigral Degeneration," Japan J. Rehabil. Med., Vol. 41, No. 1, pp. 48-51, (January 18, 2004).	ABS.
	A102	OHASHI, "Autonomic disorders in spinal cord injured patients," Journal of Clinical Rehabilitation, Vol. 6, No. 12, pp. 1186-1191, (December 15, 1997).	

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ning of each regular issue of the PCT Gazette.***WO 02/100404 A2**(54) Title: **FORMULATIONS AND METHODS FOR THE TREATMENT OF HOT FLUSHES**

(57) Abstract: The present invention is concerned with formulations for use in a method of suppressing hot flushes, especially hot flushes in hypo-estrogenic females and androgen-deprived males. More particularly the invention relates to a pharmaceutical formulation for use in a method of suppressing hot flushes, said method comprising the administration of the formulation so as to provide on a daily basis a combination of: a. serotonin re-uptake inhibitor in an amount which is equivalent to less than 100 mg trazodone and b. vitamin B6 component, in an amount effective to reduce the incidence and/or intensity of hot flushes. Another aspect of the invention relates to pharmaceutical formulations comprising a combination of a. serotonin re-uptake inhibitor in an amount which is equivalent to 0.6 to 45 mg, preferably 0.6 to 24 mg trazodone and b. 0.005 to 5 nmoles of vitamin B6 component, and additionally comprising pharmaceutically acceptable excipient.

## FORMULATIONS AND METHODS FOR THE TREATMENT OF HOT FLUSHES

## FIELD OF THE INVENTION

5

The present invention is concerned with a method of treating hot flushes, particularly hot flushes in hypo-estrogenic females, such as (peri-)menopausal and post-menopausal females, and also in androgen-deprived males. More particularly the invention relates to methods of suppressing hot flushes by administering a combination of serotonin re-uptake inhibitor and vitamin B6 component in an amount effective to reduce the incidence and/or intensity of hot flushes.

10

The invention also relates to pharmaceutical formulations comprising a combination of serotonin re-uptake inhibitor and vitamin B6 component.

15

## BACKGROUND OF THE INVENTION

Serotonin (5-hydroxytryptamine) is a neurotransmitter that is found in relatively high concentrations in the lateral gray horns of the spinal cord and in a number of areas in the brain. A system of serotonin-containing neurons that have their cell bodies in the raphe nuclei of the brain stems project to portions of the hypothalamus, the limbic system, the neocortex and the spinal cord. It has been demonstrated that serotonin interacts with a great number of receptors in the brain and controls or affects processes which regulate many bodily organs and functions.

20

Serotonin is an important chemical messenger participating in the transmission of nerve impulses in the brain. These messengers are released at specific sites on pre-synaptic cells and received, to complete transmission of the impulse, at specific sites on post-synaptic cells. Their effect is then terminated by metabolism or by uptake into the pre-synaptic cells. In addition, some of the released serotonin is inactivated by monoamine oxidase to form 5-hydroxyindoleacetic acid. This is the principal urinary metabolite of serotonin.

25

30

Serotonin is formed in the body by hydroxylation and decarboxylation of the essential amino acid L-tryptophan. In the biosynthesis of serotonin from L-tryptophan, L-tryptophan is

WO 02/100404

PCT/NL02/00382

hydroxylated in the presence of the enzyme tryptophan hydroxylase to form the intermediate product L-5-hydroxytryptophan. This intermediate product is decarboxylated in the presence of the enzyme 5-hydroxytryptophan decarboxylase to form serotonin.

5 Serotonin deficiencies in the brain have been associated with a number of mainly psychological disorders such as (endogenous) depression, insomnia, excessive appetite and lowered pain threshold. Recent publications have shown that hot flushes in (peri)menopausal and post-menopausal females may also be related to reduced levels of serotonin.

10 An important discovery in medicinal chemistry of the past decades are the serotonin re-uptake inhibitors (SRI's), which are particularly effective in the treatment of depression. SRI's increase the availability of serotonin in the synapse by reducing the re-uptake of serotonin by the serotonin uptake carrier (transporter protein). Dysfunction of the serotonin neurons resulting from excessive uptake results in depression, as well as other pathologies of the central nervous system.

15 Among the commercially available SRI's are fluoxetine, nefazodone, sertraline, venlafaxine, citalopram, fluvoxamine, paroxetine and trazodone. While the primary activity of these drugs is the inhibition of the re-uptake of serotonin, the cascade of monoamine processes in the brain connects serotonin with both norepinephrine and dopamine. Thus, the increase of availability of serotonin may result in increased availability of norepinephrine and dopamine as well.

20 SRI's have also found application in methods for suppressing hot flushes in methods of decreasing hot flushes in females. EP-A 0 943 329 (Eli Lilly and Company) describes a method for decreasing hot flushes in a human female by administering fluoxetine to that female. An effective dose of fluoxetine is said to range from about 0.001 mg/kg to about 5 mg/kg body weight, per day. The total dosage (per day) of fluoxetine is usually in the range of  
25 about 5 mg to 80 mg per day.

Since the commercial introduction of the first SRI's in the early eighties these pharmaceutical components have found widespread application, particularly as anti-depressants. Despite this success it is well recognised that, due to a number of undesirable side-effects, such SRI's are to be applied with caution. Examples of side-effects that have  
30 reported in connection with the use of SRI's are: effects on sexual function, gastrointestinal symptoms such as nausea, vomiting and diarrhoea, headache, nervousness, insomnia and somnolence (Van den Berg, "Comparing SSRI's; from chemistry to clinical choice", Human

WO 02/100404

PCT/NL02/00382

Psychopharmacol. (1995), 10, 199-209 and McManus et al., 'Nausea and vomiting associated with selective serotonin re-uptake inhibitors - incidence, mechanisms and management', CNS Drugs (1997), 8, 394-401).

In view of the aforementioned side-effects there still is a need for pharmaceutical formulations which deliver the same functionality as existing SRI's, but with less pronounced side effects. It is an objective of the present invention to make available pharmaceutical formulations that comprise one or more SRI's in combination with vitamin B6 component (e.g. vitamin B6) in an amount which effectively enhances the functionality of said one or more SRI's, thus allowing similar results (in terms of suppression of hot flushes) to be achieved at a significantly lower dosage.

US 4,596,807 (Crosby) describes a method for controlling pain, depression and sedation, which method comprises administering a composition comprising a serotonin precursor, such as L-tryptophan or L-5-hydroxytryptophan in an amount effective to increase the brain serotonin to a supra normal level, in combination with a SRI in an amount effective to inhibit the re-uptake of serotonin. The composition may additionally comprise vitamin B6 (pyridoxine) and vitamin C (ascorbic acid) so as to aid biosynthesis of serotonin in case of patients suffering from vitamin depletion. In accordance with this patent, administration of the composition is desirably effected in 1-4 portions daily, delivering 100-800 mg per day of SRI and 40-400 mg per day of the pyridoxine.

US 5,885,976 (Sandyk) is concerned with methods for the treatment of neurological and mental disorders related to deficient serotonin neurotransmission and impaired pineal melatonin functions. The method described comprises administering an effective amount of a composition which increases serotonin transmission followed by the application to the brain of a sufficient amount of an AC pulsed magnetic field to treat the disorder. It is mentioned that the composition may contain a stimulant of serotonin synthesis which is vitamin B1, vitamin B3, vitamin B6, biotin, S-adenosyl methionine, vitamin D, folic acid, ascorbic acid, magnesium, coenzyme Q10, piracetam, or mixtures of two or more thereof. Furthermore it is stated that the composition can include a SRI which is sertraline, nefazodone, trazodone, fluoxetine or a mixture thereof. The ranges of daily dosage levels specifically mentioned for a number of SRI's in this patent broadly cover the range of 25-600 mg.

US 5,254,572 (Serfontein) relates to a method of treatment or prophylaxis of depressed or inadequate intracellular pyridoxal phosphate levels in a patient resulting from a

WO 02/100404

PCT/NL02/00382

condition, wherein the pyridoxine-pyridoxal phosphate pathway is disturbed or insufficient. The deficiencies are counteracted by the administration of pyridoxal or a precursor of pyridoxal which *in vivo* is rapidly converted into pyridoxal. The methods described are said to be particularly suitable for the treatment or prophylaxis of the broad category of physiological shock, including myocardial infarction.

## SUMMARY OF THE INVENTION

The present invention provides formulations and methods for suppressing hot flushes (also sometimes referred to as hot flashes). The pharmaceutical formulations according to the invention comprise one or more serotonin uptake inhibitors (SRI's) as well as a vitamin B6 component that is capable of enhancing the suppressing action of said one or more SRI's, i.e. acting as a potentiating agent. As a result of the presence of said vitamin B6 component, the levels of SRI needed to achieve the desired suppression can be reduced significantly. Thus the formulations and methods according to the present invention are characterised by the application of relatively low doses of SRI.

Applicants have surprisingly found that vitamin B6 components can advantageously be used in combination with SRI's to increase the effectiveness of these components in suppressing hot flushes. Thus vitamin B6 effectively potentiates the effectiveness of the SRI's against hot flushes. Hence vitamin B6 components are referred to in this document as potentiating agents. The effectiveness of the present method is best demonstrated by the low concentration levels of SRI required to obtain effective suppression of hot flushes. Whereas EP-A 0 943 329 (Eli Lilly) mentions the use of fluoxetine against hot flushes in a concentration range of 1-200 mg per day, and more specifically in the range of 15-40 mg per day, the compositions according to the invention are effective when they contain fluoxetine in quantities that are in the range of 0.1-15 mg per day.

Although the combined use of SRI's and vitamin B6, in areas other than the treatment of hot flushes, has been described in the prior art, it has not been recognised before that, in case of treatment of hot flushes, vitamin B6 has the capability of enhancing the action of SRI's in a way which allows application of SRI's at lower than usual dosage levels. The prior art publications which describe the combined use of SRI's and vitamin B6 teach to employ

SRI's at conventional dosage levels. No suggestions are made in these publications that vitamin B6 may act as a potentiating agent for SRI's.

## 5 DETAILED DESCRIPTION OF THE INVENTION

In one embodiment the present invention is concerned with a pharmaceutical formulation comprising a combination of

- a. serotonin re-uptake inhibitor in an amount which is equivalent to 0.6 to 45 mg, preferably  
10 0.6 to 24 mg trazodone, more preferably 1 to 20 mg trazodone,
  - b. 0.005 to 5 mmoles of vitamin B6 component,
- and additionally comprising pharmaceutically acceptable excipient.

The term "serotonin re-uptake inhibitor", also sometimes referred to as "serotonin specific (or selective) re-uptake inhibitor (or SSRI)" encompasses those re-uptake inhibitors  
15 that are capable of significantly inhibiting re-uptake of serotonin by blocking its transporter protein, by inhibiting monoamine oxidase and/or by (selectively) blocking cerebral serotonin receptors.

The term "vitamin B6 components" as used throughout this document encompasses any components which *in vivo*, particularly once these components or their metabolites have  
20 entered the bloodstream, are converted into pyridoxal or a pyridoxal salt. Particularly useful are vitamin B6 components that *in vivo* are converted for at least 10 mol% into pyridoxal or a pyridoxal salt within 24 hours after administration.

Inside living human and animal cells, pyridoxal phosphate and pyridoxamine phosphate are the biologically active forms of vitamin B6, acting as a co-enzymes in more  
25 than 100 biological reactions. In the form of pyridoxal 5'-phosphate and pyridoxamine 5'-phosphate, vitamin B6 acts as the coenzyme of a series of enzymes, which catalyse transamination, decarboxylation, deamination, desulphydration and the cleavage or synthesis of amino acids. The aminotransferases represent an important link between amino acid, carbohydrate and fatty acid metabolism and the energy-producing citric acid cycle. The  
30 decarboxylases convert amino acids to the corresponding biogenic amines, such as histamine, hydroxytyramine, serotonin,  $\gamma$ -aminobutyric acid, ethanolamine and taurine, some of which are substances of high physiological activity [regulation of the blood vessel diameter, neurohormonal actions, essential components of phospholipids and bile acids].

WO 02/100404

PCT/NL02/00382

In accord with the general importance these enzymatic reactions take place in virtually all organs most intensively in the liver, heart and brain. (Lit. Vitamin Compendium; Roche, Vitamins and Chemicals Department. F. Hoffmann- La Roche and Co. Ltd, Basle, Switzerland).

5 In a preferred embodiment of the invention the pharmaceutical formulation is suitable for oral, enteral or topical administration. Most preferably said formulation is for oral administration.

In order to achieve appreciable increases in cerebral serotonin levels, the formulation will usually contain SRI in an amount which is equivalent to at least 1 mg trazodone and  
10 vitamin B6 component in an amount of 0.005 to 5 mmoles. More preferably the amount of SRI utilised is equivalent to 4-20 mg trazodone. The most preferred amount of vitamin B6 component is in the range of 0.01 to 2 mmoles. Formulations for oral dosage containing the aforementioned amounts of SRI and vitamin B6 component are particularly suited for at least once daily administration.

15 Another embodiment of the present invention is related to a pharmaceutical formulation for use in a method of suppressing hot flushes, said method comprising the administration of the formulation so as to provide on a daily basis a combination of:

a. serotonin re-uptake inhibitor in an amount which is equivalent to less than 100 mg trazodone and

20 b. vitamin B6 component,

in an amount effective to reduce the incidence and/or intensity of hot flushes. The method of the invention preferably does not include the application to the brain of an AC pulsed magnetic field of at least 7.5 picotesia flux density for at least 15 minutes. More preferably the method does not include the application of an AC pulsed magnetic field of at  
25 least 7.5 picotesia. Most preferably the method does not include the application of an AC pulsed magnetic field at all.

The term "on a daily basis", when used in connection with a mentioned dosage amount, should not be interpreted restrictedly. For instance, the above mentioned requirement that the administration of the present formulation is to provide, on a daily basis, SRI in an  
30 amount of less than 100 mg trazodone, encompasses a protocol wherein trazodone is administered once a week, provided the dosage is less than 700 mg, i.e. such that the average daily dose is less than 100 mg trazodone.

Co-administration of SRI's with vitamin B6 component was found to be very effective against hot flushes in both females and males. Particularly good results are obtained with the present method in hypo-estrogenic females, particularly (peri-)menopausal and post-menopausal females, and in androgen-deprived males. Here by co-administration is meant that on the one hand SRI and on the other the vitamin B6 component are administered during a time frame wherein the respective periods of pharmacological activity overlap. Thus the term includes sequential as well as simultaneous administration. Since SRI and vitamin B6 component may be co-administered in a sequential as well as in a coextensive fashion the term "pharmaceutical formulation" as used throughout this document should be understood to encompass pharmaceutical kits which comprise separate dosage units for the SRI component and the vitamin B6 component.

The benefits of the formulations according to the invention are particularly pronounced when said formulations are used in a method of controlling hot flushes. Hot flushes are not only experienced by (peri-)menopausal and post-menopausal females, but also occur in hypogonadism, after bilateral ovariectomy and occasionally in the premenstrual syndrome (as a result of hypo-estrogenism). Also androgen-deprived males have been reported to suffer from hot flushes. A hot flush is characterised by a sudden sensation of heat or burning which starts in the head and neck area and then passes, often in waves, over the entire body, but particularly marked in the head, neck, upper chest and back. In most cases hot flushes are accompanied by profuse sweating. The exact pathophysiology of the hot flush is still unknown but it appears to be related to an alteration in the set point temperature in the hypothalamus, the area in which thermosensitive neurons or temperature guardian neurons have been found. Hot flushes are experienced in those periods of the female life after puberty when estrogen levels are low. Hormone replacement therapy (HRT) is thus the first choice for treatment of hot flushes. However, this treatment is not always accepted, may cause undesirable side effects, or is contraindicated for a variety of reasons.

The combination of SRI and vitamin B6 component is deemed to be a good alternative to HRT because HRT has a series of disadvantages. Firstly in women with an uterus the recurrence of menses and vaginal bleeding may be unacceptable. Secondly there are many females who, for a variety of reasons, have serious reservations about HRT-treatment. Thirdly HRT may cause side-effects such as nausea, vomiting, breast tension, headache, mood disturbances, fluid retention, bloating, breakthrough vaginal bleeding, liver function

WO 02/100404

PCT/NL02/00382

trazodone. Most preferably the maximum daily amount of SRI provided by the method is equivalent to less than 75 mg trazodone.

The present formulations preferably do not contain a narcotic, specifically not a narcotic selected from the group consisting of codeine, oxycodone, propoxyphene, pentazocine, morphine, meperidine, levorphanol, menthadone and mixtures thereof, in an amount effective to produce analgesia.

The present method of treatment preferably comprises administration of SRI in a daily amount which is equivalent to between 0.01 and 1 mg trazodone per kg bodyweight and between 0.0001 and 0.2 mmoles of the vitamin B6 component per kg bodyweight. More preferably the SRI is administered in an amount of between 0.02 and 0.8 mg trazodone equivalent/kg/day and the vitamin B6 component in an amount between 0.0004 and 0.1 mmoles/kg/day.

Vitamin B6 components which can suitably be used in accordance with the present invention are those selected from the group consisting of pyridoxal, pyridoxamine, acetals of pyridoxal, condensation products arising from the reaction of the aldehyde group of pyridoxal with an amine, and addition salts of any of the foregoing members of the group with pharmaceutically acceptable salts. The term "pharmaceutically acceptable salts" includes salts with pharmaceutically acceptable acids of bases, e.g. acids such as sulphuric, hydrochloric, nitric, phosphoric acid, etc. or bases such as alkali or alkaline earth metal hydroxides, ammonium hydroxides, alkyl ammonium hydroxides etc.

Pyridoxine HCl is the pharmaceutically most widely used form of vitamin B6. However, it has a short half-life in blood *in vivo* as it is readily excreted and/or converted into physiologically unavailable compounds. Also pyridoxine must pass through a chain of biochemical reactions before it can enter the cells and finally end up there as required in the form of active vitamin B6, i.e. pyridoxal phosphate or pyridoxamine phosphate. Thus it can be advantageous to use a vitamin B6 component such as pyridoxal or pyridoxal salt. Preferably, however, the vitamin B6 component used in the present formulation and method is pyridoxine, more preferably the hydrochlorate of pyridoxine, i.e. pyridoxine HCl).

In order to obtain a significant beneficial effect from the co-administration of SRI and vitamin B6 component, it is advisable to apply the vitamin B6 component and SRI in a dosage ratio which is in the range of 0.002 to 1 mmole/mg, more preferably within the range of 0.01 to 0.5 mmole/mg trazodone equivalent.

WO 02/100404

PCT/NL02/00382

In a preferred embodiment of the present invention the SRI's employed are selected from the group selected of citalopram, fluoxetine, norfluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, zimelidine, femoxetine, trazodone, nefazodone, mirtazapine, pharmaceutically acceptable salts of these inhibitors and mixtures thereof. Most preferably the

5 SRI's are selected from the group consisting of citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, trazodone, nefazodone, mirtazapine, pharmaceutically acceptable salts of these inhibitors and mixtures thereof. It is noted that the SRI's used in present formulations may be present in the form of a racemic mixture as well as in the form of a stereo-enantiomer.

10 Throughout this document amounts of SRI's have been defined in terms of trazodone equivalents. In order to facilitate the translation of given amounts of trazodone into the equivalent amounts of another SRI the following table provides the multiplication factors that are to be used:

	Trazodone conversion factor
citalopram	0.15
fluoxetine	0.15
fluvoxamine	0.7
paroxetine	0.15
sertraline	0.3
venlafaxine	0.5
trazodone	1.0
mirtazapine	0.2
nefazodone	1.3

15

With the help of the above table it can be calculated that 100 mg trazodone is equivalent to 30 mg sertraline or 15 mg fluoxetine.

In another preferred embodiment of the present invention the pharmaceutical formulation additionally comprises at least 300 mg, more preferably from 500 to 10,000 mg

20 of a serotonin precursor selected from the group consisting of L-tryptophan, 5-hydroxytryptophan, precursors of these tryptophan substances and mixtures thereof. The inclusion of the latter precursors may assist in alleviating serotonin deficiency since serotonin

WO 02/100404

PCT/NL02/00382

is biosynthesised from tryptophan through the following metabolic chain:

tryptophan > 5-hydroxytryptophan > 5-hydroxytryptamine > serotonin.

Tryptophan is usually not transported in the blood in a free state, but rather bound to or complexed with blood serum albumin. Tryptophan is the only circulating amino acid that is significantly bound to human blood serum albumin. It has been shown that salicylates displace tryptophan from its protein binding site on albumin in blood plasma thereby raising the free, circulating tryptophan concentration in blood. This free or unbound tryptophan is more easily converted to serotonin than the bound form. Hence the present pharmaceutical formulation may advantageously contain as an additional component a salicylate. Preferably the formulation comprises at least 0.05 mmoles of such a salicylate, more preferably from 0.1 to 1.5 mmoles of the salicylate. Here the term "salicylate" includes both the acid and the salt. The salicylate is preferably selected from the group consisting of sodium salicylate, choline salicylate, magnesium salicylate and mixtures thereof.

Yet another component which may additionally be included in the present formulation is a component that acts as a stimulant of the serotonin receptor, such as buspirone. Hence in another preferred embodiment the formulation comprises at least 10  $\mu$ moles, preferably from 20 to 300  $\mu$ moles of buspirone.

The pharmaceutical formulations for use in the method of the invention can be solid or semi-solid dosage forms such as tablets, capsules, cachets, pellets, pills, powders and granules, as well as fluid dosage forms such as solutions, emulsions, suspensions, ointments, pastes, creams, gels, jellies and foams. In addition to the pharmacologically active components, the formulation according to the invention contains pharmaceutically acceptable excipient, usually in an amount of between 50 and 99.9 wt.%.

Tablets and equivalent solid and semi-solid dosage forms can suitably contain excipients such binders (e.g. hydroxypropylmethyl cellulose, polyvinyl-pyrrolidone, other cellulosic materials and starch), diluents (e.g. lactose and other sugars, starch, dicalcium phosphate and cellulosic materials), disintegrating agents (e.g. starch polymers and cellulosic materials) and lubricating agents (e.g., stearates and talc).

Transdermal delivery systems include patches, gels, tapes and creams, and can contain excipients such as solubilisers, permeation enhancers (e.g. fatty acids, fatty acid esters, fatty alcohols and amino acids), hydrophilic polymers (e.g. polycarbophil and polyvinyl pyrillidine and adhesives and tackifiers (e.g. polyisobutylenes, silicone-based adhesives, acrylates

WO 02/100404

PCT/NL02/00382

and polybutene).

Transmucosal delivery systems include patches, tablets, suppositories, pessaries, gels, and creams, and can contain excipients such as solubilizers and enhancers (e.g. propylene glycol, bile salts and amino acids), and other vehicles (e.g. polyethylene glycol, fatty acid esters and derivatives, and hydrophilic polymers such as hydroxypropylmethyl cellulose and hyaluronic acid).

Injectable delivery systems include solutions, suspensions, gels, microspheres and polymeric injectables, and can comprise excipients such as solubility-altering agents (e.g. ethanol, propylene glycol and sucrose) and polymers (e.g. polycaprylactones, and PLGA's).

Implantable systems include rods and discs, and can contain excipients such as PLGA and polycapryl lactone.

Other delivery systems that can be used for administering the pharmaceutical composition of the invention include intranasal delivery systems such as sprays and powders, and sublingual delivery systems.

15

#### EXAMPLE

A clinical study is conducted with 12 peri-menopausal women experiencing at least 40-50 hot flushes per week.

The study is designed as a so called double blind, cross-over study. During the study the medication is orally administered once a day. The visual aspects of the medication used is always the same, i.e. these aspects offer no clues as to the nature of the medication. The volunteers are asked to record the number of hot flushes they experience in a diary (at least 1 entry per day).

During an initial period of 56 days (days 1-56), all 12 participants receive the same medication, i.e. 20 mg Fluoxetine HCl. Subsequently, the twelve women are randomly divided into two groups, i.e. group A with six women and group B with six women.

Group A is administered the combination of 5mg Fluoxetine HCl + 50mg vitamin B6 during 112 days (days 57-168) and further the combination of 5mg Fluoxetine HCl + placebo during another 112 days (days 169-281). Group B is administered the combination of 5mg Fluoxetine HCl + placebo during days 57-168 and the combination of 5mg Fluoxetine HCl + 50mg vitamin B6 during days 169-281.

Results show that during the period of the first 56 days, the number of hot flushes

WO 02/100404

PCT/NL02/00382

experienced per day, decreases substantially over time, indicating that 20 mg Fluoxetine HCl as such is efficacious in suppressing hot flushes.

For group A the daily number of hot flushes experienced during days 57-168 is of the same order of magnitude as before the change of medication. During days 169-281, the  
5 number of hot flushes increases again over time.

For group B, the daily number of hot flushes experienced during days 57-168 increases over time. However, during days 169-281, when vitamin B6 is taken instead of placebo, the number of hot flushes decreases to substantially lower levels.

WO 02/100404

PCT/NL02/00382

## CLAIMS

1. A pharmaceutical formulation for use in a method of suppressing hot flushes, said method comprising the administration of the formulation so as to provide on a daily basis a  
5 combination of :
- a. serotonin re-uptake inhibitor in an amount which is equivalent to less than 100 mg trazodone and
  - b. vitamin B6 component,
- in an amount effective to reduce the incidence and/or intensity of hot flushes.
- 10
2. A pharmaceutical formulation according to claim 1, wherein the method comprises administration of the formulation so as to provide on a daily basis serotonin re-uptake inhibitor in an amount equivalent to 0.6-80 mg trazodone.
- 15
3. A pharmaceutical formulation according to claim 1 or 2, wherein the method comprises administration of the formulation so as to provide on a daily basis between 0.005 and 5 mmoles of the vitamin B6 component.
4. A pharmaceutical formulation according to any one of claim 1-3 for use in a method  
20 of suppressing hot flushes in hypo-estrogenic females or androgen-deprived males.
5. A pharmaceutical formulation according to any one of claims 1-4, wherein the method comprises at least once daily administration of the formulation.
- 25
6. A pharmaceutical formulation according to any one of claims 1-5, wherein the method comprises administration of serotonin re-uptake inhibitor in a daily amount which is equivalent to between 0.01 and 1 mg trazodone per kg bodyweight and between 0.0001 and 0.2 mmoles of the vitamin B6 component per kg bodyweight.
- 30
7. A pharmaceutical formulation comprising a combination of
- a. serotonin re-uptake inhibitor in an amount which is equivalent to 0.6 to 45 mg, preferably 0.6 to 24 mg trazodone and

WO 02/100404

PCT/NL02/00382

b. 0.005 to 5 mmoles of vitamin B6 component,  
and additionally comprising pharmaceutically acceptable excipient.

8. A pharmaceutical formulation according to claim 7, wherein the formulation  
comprises serotonin re-uptake inhibitor in an amount which is equivalent to at least 1 mg  
trazodone and vitamin B6 component in an amount of 0.01 to 2 mmoles.

9. A pharmaceutical formulation according to any one of claims 1-8, wherein the vitamin  
B6 component is selected from the group consisting of pyridoxal, pyridoxamine, acetals of  
pyridoxal, condensation products arising from the reaction of the aldehyde group of pyridoxal  
with an amine, and addition salts of any of the foregoing members of the group with  
pharmaceutically acceptable salts,

10. A pharmaceutical formulation according to any one of claims 1-9, wherein the dosage  
ratio of vitamin B6 component to serotonin re-uptake inhibitor is in the range of 0.002 to 1  
mmole/mg trazodone equivalent.

11. A pharmaceutical formulation according to any one of claims 1-10, wherein the  
serotonin re-uptake inhibitor is selected from the group selected of citalopram, fluoxetine,  
norfluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, zimelidine, femoxetine,  
trazodone, nefazodone, mirtazapine, pharmaceutically acceptable salts of these inhibitors and  
mixtures thereof.

12. A pharmaceutical formulation according to any one of claims 1-11, wherein the  
formulation comprises at least 300 mg of a serotonin precursor selected from the group  
consisting of L-tryptophan, 5-hydroxytryptophan, precursors thereof and mixtures thereof.

13. A pharmaceutical formulation according to any one of claims 1-12, wherein the  
formulation comprises at least 0.05 mmoles of a salicylate.

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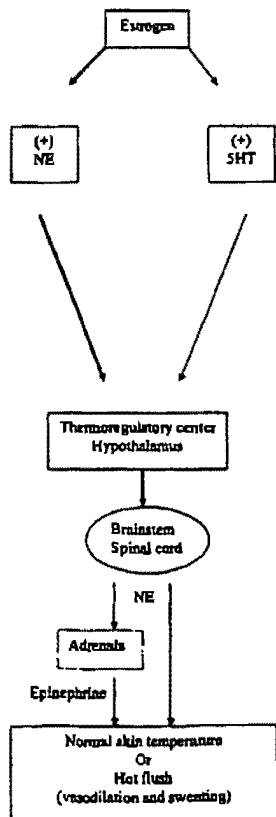
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(54) Title: USE OF NOREPINEPHRINE REUPTAKE MODULATORS FOR PREVENTING AND TREATING VASOMOTOR SYMPTOMS

(57) Abstract: The present invention relates to the use of compounds and composition of com-  
pounds that modulate norepinephrine levels for the prevention and treatment of vasomotor symp-  
toms, such as hot flush, caused by, *inter alia*, thermoregulatory dysfunctions.



WO 2004/035058 A1

WO 2004/035058 A1



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## USE OF NOREPINEPHRINE REUPTAKE MODULATORS FOR PREVENTING AND TREATING VASOMOTOR SYMPTOMS

### CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of U.S. Application Serial No. 60/418,591, filed October 15, 2002, the disclosure of which is incorporated herein by reference in its entirety.

### FIELD OF THE INVENTION

[0002] The present invention relates to the use of compounds and composition of compounds that modulate norepinephrine levels for the prevention and treatment of, *inter alia*, vasomotor symptoms (VMS).

### BACKGROUND OF THE INVENTION

[0003] Vasomotor symptoms (VMS), referred to as hot flushes and night sweats, are the most common symptoms associated with menopause, occurring in 60% to 80% of all women following natural or surgically-induced menopause. VMS are likely to be an adaptive response of the central nervous system (CNS) to declining sex steroids. To date, the most effective therapies for VMS are hormone-based treatments, including estrogens and/or some progestins. Hormonal treatments are very effective at alleviating VMS, but they are not appropriate for all women. It is well recognized that VMS are caused by fluctuations of sex steroid levels and can be disruptive and disabling in both males and females. A hot flush can last up to thirty minutes and vary in their frequency from several times a week to multiple occurrences per day. The patient experiences a hot flash as a sudden feeling of heat that spreads quickly from the face to the chest and back and then over the rest of the body. It is usually accompanied by outbreaks of profuse sweating. It may sometimes occur several times an hour, and it often occurs at night. Hot flushes and outbreaks of sweats occurring during the night can cause sleep deprivation. Psychological and emotional symptoms observed, such as

nervousness, fatigue, irritability, insomnia, depression, memory loss, headache, anxiety, nervousness or inability to concentrate are considered to be caused by the sleep deprivation following hot flush and night sweats (Kramer *et al.*, In: Murphy *et al.*, 3<sup>rd</sup> Int'l Symposium on Recent Advances in Urological Cancer Diagnosis and Treatment-Proceedings, Paris, France: SCI: 3-7 (1992)).

**[0004]** Hot flushes may be even more severe in women treated for breast cancer for several reasons: 1) many survivors of breast cancer are given tamoxifen, the most prevalent side effect of which is hot flush, 2) many women treated for breast cancer undergo premature menopause from chemotherapy, 3) women with a history of breast cancer have generally been denied estrogen therapy because of concerns about potential recurrence of breast cancer (Loprinzi, C.L., *et al.*, *Lancet*, 2000, 356(9247): 2059-2063).

**[0005]** Men also experience hot flushes following steroid hormone (androgen) withdrawal. This is true in cases of age-associated androgen decline (Katovich, *et al.*, *Proceedings of the Society for Experimental Biology & Medicine*, 1990, 193(2): 129-35) as well as in extreme cases of hormone deprivation associated with treatments for prostate cancer (Berendsen, *et al.*, *European Journal of Pharmacology*, 2001, 419(1): 47-54. As many as one-third of these patients will experience persistent and frequent symptoms severe enough to cause significant discomfort and inconvenience.

**[0006]** The precise mechanism of these symptoms is unknown but generally is thought to represent disturbances to normal homeostatic mechanisms controlling thermoregulation and vasomotor activity (Kronenberg *et al.*, "Thermoregulatory Physiology of Menopausal Hot Flashes: A Review," *Can. J. Physiol. Pharmacol.*, 1987, 65:1312-1324).

**[0007]** The fact that estrogen treatment (e.g. estrogen replacement therapy) relieves the symptoms establishes the link between these symptoms and an estrogen deficiency. For example, the menopausal stage of life is associated with a wide range of other acute symptoms as described above and these symptoms are

generally estrogen responsive.

[0008] Although VMS are most commonly treated by hormone therapy (orally, transdermally, or via an implant), some patients cannot tolerate estrogen treatment (Berendsen, *Maturitas*, 2000, 36(3): 155-164, Fink *et al.*, *Nature*, 1996, 383(6598): 306). In addition, hormone replacement therapy is usually not recommended for women or men with or at risk for hormonally sensitive cancers (e.g. breast or prostate cancer). Thus, non-hormonal therapies (e.g. fluoxetine, paroxetine [SRIs] and clonidine) are being evaluated clinically. WO9944601 discloses a method for decreasing hot flushes in a human female by administering fluoxetine. Other options have been studied for the treatment of hot flashes, including steroids, alpha-adrenergic agonists, and beta-blockers, with varying degree of success (Waldinger *et al.*, *Maturitas*, 2000, 36(3): 165-168).

[0009] It has been reported that  $\alpha_2$ -adrenergic receptors play a role in thermoregulatory dysfunctions (Freedman *et al.*, *Fertility & Sterility*, 2000, 74(1): 20-3). These receptors are located both pre and post synaptically and mediate an inhibitory role in the central and peripheral nervous system. There are four distinct subtypes of the adrenergic  $\alpha_2$  receptors, i.e., are  $\alpha_{2A}$ ,  $\alpha_{2B}$ ,  $\alpha_{2C}$  and  $\alpha_{2D}$  (Mackinnon *et al.*, *TIPS*, 1994, 15: 119; French, *Pharmacol. Ther.*, 1995, 68: 175). It has been reported that a non-select  $\alpha_2$ -adrenoceptor antagonist, yohimbine, induces a flush and an  $\alpha_2$ -adrenergic receptor agonist, clonidine, alleviates the yohimbine effect (Katovich, *et al.*, *Proceedings of the Society for Experimental Biology & Medicine*, 1990, 193(2): 129-35, Freedman *et al.*, *Fertility & Sterility*, 2000, 74(1): 20-3). Clonidine has been used to treat hot flush. However, using such treatment is associated with a number of undesired side effects caused by high doses necessary to abate hot flash described herein and known in the related arts.

[0010] Given the complex multifaceted nature of thermoregulation and the interplay between the CNS and PNS in maintaining thermoregulatory homeostasis, multiple therapies and approaches can be developed to target vasomotor symptoms. The present invention focuses on novel methods of recovery of activity of NE by

modulating the noradrenergic system.

## SUMMARY OF THE INVENTION

[0011] The invention is directed to compounds and compositions containing compounds to modulate norepinephrine levels for the prevention and treatment of, *inter alia*, vasomotor symptoms (VMS) caused by, for example, thermoregulatory dysfunctions, such as those experienced by pre-, peri- and post menopausal females and naturally, chemically or surgically andropausal males. In some aspects, the present invention relates to the use of compounds and compositions of norepinephrine reuptake inhibitors alone or in combination with serotonin reuptake inhibitors for the modulation of the norepinephrine system. In other aspects, the present invention relates to the use of compounds and composition of compounds having norepinephrine reuptake inhibitor activity in combination with adrenergic $\alpha_2$  receptor antagonist activity, as either a single compound or a combination of compounds. In yet other embodiments, the invention relates to the use of compounds and composition of compounds having dual NRI/SRI activity.

[0012] In one embodiment, the present invention is directed to methods for treating or preventing vasomotor symptoms in a subject in need thereof, comprising the step of:

administering to said subject a composition, comprising a therapeutically effective amount of at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof.

[0013] In preferred embodiments, the compound has a selectivity ratio of SERT:NET of less than about 1,000:1. In other preferred embodiments, the compound has a selectivity ratio of SERT:NET of greater than about 2:1, more preferably, greater than about 5:1, and even more preferably, greater than about 10:1.

[0014] In other preferred embodiments, the invention is directed to methods wherein the composition further comprises a therapeutically effective amount of at

least one serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof. In certain preferred embodiments, the norepinephrine reuptake inhibitor and the serotonin reuptake inhibitor are administered concurrently.

[0015] In yet other preferred embodiments, the invention is directed to methods wherein the composition further comprises a therapeutically effective amount of at least one adrenergic $\alpha_2$  receptor antagonist or a pharmaceutically acceptable salt thereof. In certain preferred embodiments, the norepinephrine reuptake inhibitor and the adrenergic $\alpha_2$  receptor antagonist are administered simultaneously or concurrently. In certain preferred embodiments, the adrenergic $\alpha_2$  receptor antagonist is selective for the adrenergic $\alpha_{2A}$  receptor, adrenergic $\alpha_{2B}$  receptor, adrenergic $\alpha_{2C}$  receptor, or adrenergic $\alpha_{2D}$  receptor.

[0016] In yet other embodiments, the invention is directed to methods for treating or preventing vasomotor symptoms in a subject in need thereof, comprising the step of:

administering to said subject a therapeutically effective amount of at least one dual NRI/SRI compound or pharmaceutically acceptable salt thereof, wherein said amount is less than about 37.5 mg/day.

[0017] In other embodiments, the invention is directed to pharmaceutical compositions, comprising:

- a. at least one norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof;
- b. at least one serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof; and
- c. at least one pharmaceutically acceptable carrier.

[0018] In other embodiments, the invention is directed to pharmaceutical compositions, comprising:

- a. at least one norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof;

- b. at least one adrenergic $\alpha_2$  receptor antagonist or a pharmaceutically acceptable salt thereof; and
- c. at least one pharmaceutically acceptable carrier.

In certain preferred embodiments, the norepinephrine reuptake inhibitor and adrenergic $\alpha_2$  receptor antagonist are a single compound. In other preferred embodiments, norepinephrine reuptake inhibitor and adrenergic $\alpha_2$  receptor antagonist are a combination of two or more compounds.

## BRIEF DESCRIPTION OF THE DRAWINGS

[0019] The invention can be more fully understood from the following detailed description and the accompanying drawings that form a part of this application.

[0020] **Figure 1** is an overview of estrogen action on norepinephrine/serotonin mediated thermoregulation.

[0021] **Figure 2** is a schematic representation of the interactions of norepinephrine and serotonin and their respective receptors (5-HT<sub>2A</sub>,  $\alpha_1$  and  $\alpha_2$ -adrenergic).

[0022] **Figures 3A through 3F** are graphical representations of the effect of NRIs in alleviating vasomotor instabilities, as exemplified in **Example 1**. **Figure 3A** shows a dose response in morphine-dependent rat model of hot flush (MD model) for desipramine. **Figure 3B** shows desipramine 10 mg/kg, sc in OVX-induced thermoregulatory dysfunction telemetry model (telemetry model). **Figure 3C** shows reboxetine dose response in MD model. **Figure 3D** shows changes in TST over time in MD model for reboxetine at various doses. **Figure 3E** shows changes in TST over time in MD model for 1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol (824) at various doses. **Figure 3F** shows maximal flush for vehicle, 1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol (WY-781), and 1-[2-(dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol (WY-

867).

[0023] **Figure 4** shows NRI (desipramine) dose response in combination with SRI (fluoxetine 10 mg/kg) in morphine-dependent rat model of hot flush (referred to in **Example 2**).

[0024] **Figures 5A, 5B, 5E, 5F, 5G, 5H and 5J** show dose response of venlafaxine, DVS-233/ODV, *R*-venlafaxine, *S*-venlafaxine, *R*-ODV, *S*-ODV, and paroxetine in MD model, respectively. **Figures 5C and 5D** show venlafaxine (15 mg/kg, sc) and DVS-233 (60 mg/kg, sc) in a telemetry model (\* indicates  $p < 0.05$  compared to vehicle control) (referred to in **Example 3**).

[0025] **Figure 6** demonstrates an additive effect of an  $\alpha_2$ -adrenergic antagonist (atipamezole) in combination with desipramine on a naloxone-induced flush in the MD model (referred to in **Example 4**).

#### DETAILED DESCRIPTION OF THE INVENTION

[0026] The invention is directed to compounds and compositions containing compounds to modulate norepinephrine levels for the prevention and treatment of, *inter alia*, vasomotor symptoms (VMS) caused by, for example, thermoregulatory dysfunctions, such as those experienced by pre-, peri- and post menopausal females and naturally, chemically or surgically andropausal males. In some aspects, the present invention relates to the use of compounds and compositions of norepinephrine reuptake inhibitors alone or in combination with serotonin reuptake inhibitors for the modulation of the norepinephrine system. In other aspects, the present invention relates to the use of compounds and composition of compounds having norepinephrine reuptake inhibitor activity in combination with adrenergic  $\alpha_2$  receptor antagonist activity, either as a single compound or a combination of compounds.

[0027] It is believed that the present invention described presents a substantial breakthrough in the field of treatment, alleviation, inhibition, and/or

prevention of vasomotor instability and/or dysfunction.

[0028] When estrogen levels are low or estrogen is absent, the normal levels between NE and 5-HT is altered and this altered change in neurotransmitter levels may result in changes in the sensitivity of the thermoregulatory center. The altered chemical levels may be translated in the thermoregulatory center as heat sensation and as a response, the hypothalamus may activate the descending autonomic pathways and result in heat dissipation via vasodilation and sweating (hot flush) (Figure 1). Accordingly, the estrogen deprivation may result in altered norepinephrine activity.

[0029] Norepinephrine synthesized in perikarya of the brainstem is released at the nerve terminals in the hypothalamus and brainstem. In the hypothalamus, NE regulates the activity of neurons residing in the thermoregulatory center. In the brainstem, NE innervates serotonergic neurons (5HT), and acting via adrenergic $\alpha_1$  and adrenergic $\alpha_2$  postsynaptic receptors, it stimulates the activity of the serotonergic system. In response, 5-HT neurons also modulate the activity the thermoregulatory center and feedback to NE neurons. Via this feedback connection, 5-HT, acting via 5-HT $_{2a}$  receptors, inhibit the activity of NE neurons. Norepinephrine in the synaptic cleft is also taken up by NE transporter (NET) located in NE neurons. The transporter recycles NE and makes it available for multiple neurotransmission (Figure 2).

[0030] The present invention provides a treatment for vasomotor symptoms by methods of recovering the reduced activity of norepinephrine. Norepinephrine activity in the hypothalamus or in the brainstem can be elevated by (i) blocking the activity of the NE transporter, (ii) blocking the activity of the presynaptic adrenergic  $\alpha_2$  receptor with an antagonist, or (iii) blocking the activity of 5-HT on NE neurons with a 5-HT $_{2a}$  antagonist.

[0031] In one embodiment, it was discovered that using NRI compounds at low doses, below doses commonly used for antidepressant efficacy, results in an improved treatment to maintain normal thermoregulatory homeostasis. Furthermore,

NRI compounds in combination with SRI compounds surprisingly results in such benefits as clearer dose-related definitions of efficacy, diminished reported side effect, superior therapy due to synergistic activity, and accordingly, an improved therapeutic index. For example, high doses of NRIs or NRI/SRI compounds alone can induce vomiting, nausea, sweating, and flushes (Janowsky, *et al.*, *Journal of Clinical Psychiatry*, 1984, 45(10 Pt 2): 3-9). The present invention provides treatment or prevention of vasomotor symptoms without side effects caused by using NRI alone at high doses.

**[0032]** In one embodiment, the present invention is directed to methods for treating or preventing vasomotor symptoms in a subject in need thereof, comprising the step of:

administering to said subject a composition, comprising a therapeutically effective amount of at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof.

**[0033]** In preferred embodiments, the compound has a selectivity ratio of SERT:NET of less than about 1,000:1. In other preferred embodiments, the compound has a selectivity ratio of SERT:NET of greater than about 2:1, more preferably, greater than about 5:1, and even more preferably, greater than about 10:1.

**[0034]** In other preferred embodiments, the invention is directed to methods wherein the composition further comprises a therapeutically effective amount of at least one serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof. In certain preferred embodiments, the norepinephrine reuptake inhibitor and the serotonin reuptake inhibitor are administered concurrently. A low dose of a known NRI compound, desipramine was able to reduce the TST by 50% compared to vehicle treated rats in a naloxone-induced hot flush.

**[0035]** Examples of SRIs include, but are not limited to, fluoxetine, paroxetine, sertraline, fluvoxamine, and combinations and pharmaceutically acceptable salts thereof.

**[0036]** Examples of NRIs include, but are not limited to, maprotiline; reboxetine; norpramine, desipramine; nisooxetine; atomoxetine; amoxapine; doxepin; lofepramin; amitriptyline; 1-[1-(3-fluorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol; 1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol; 1-[2-(4-methyl-1-piperazinyl)-1-[3-(trifluoromethyl)-phenyl]ethyl]cyclohexanol; 1-[1-(4-methoxy phenyl)-2-[4-methyl-1-piperazinyl)ethyl]cyclohexanol; 1-[1-(3-chlorophenyl)-2-[4-(3-chlorophenyl)-1-piperazinyl]ethyl]cyclohexanol; 1-[1-(3-methoxyphenyl)-2-[4-phenyl methyl)-1-piperazinyl]ethyl]cyclohexanol; 1-[2-(3-chloro phenyl)-1-piperazinyl]-1-[3-methoxyphenyl)ethyl]cyclohexanol; 1-[2-[4-(6-chloro-2-pyrazinyl)-1-piperazinyl]-1-[3-methoxyphenyl)ethyl]cyclohexanol; 1-[2-[4-(phenyl methyl)-1-piperazinyl]-1-[3-(trifluoromethyl)phenyl]ethyl]cyclohexanol; 1-[1-(3-methoxyphenyl)-2-[4-[3-(trifluoro methyl)-phenyl]-1-piperazinyl]ethyl] cyclohexanol; 1-[1-(4-fluorophenyl)-2-[4-(phenylmethyl)-1-piperazinyl] ethyl] cyclohexanol; 1-[1-(3-methoxyphenyl)-2-[4-[3-(trifluoromethyl)-phenyl]-1-piperazinyl]ethyl]cyclopentanol; 1-[1-(4-fluorophenyl)-2-[4-(phenylmethyl)-1-piperazinyl]ethyl]cyclohexanol; 1-[2-(dimethylamino)-1-(3-trifluoromethyl phenyl)ethyl]cyclohexanol; 1-[1-(3-fluorophenyl)-2-(4-methyl-1-piperazinyl) ethyl]cyclohexanol; 1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl] cyclohexanol; 1-[2-dimethylamino)-1-(3-trifluoromethylphenyl) ethyl]cyclohexanol; 1-[1-(3-chlorophenyl)-2-piperazin-1-yl-ethyl]-cyclohexanol; and combinations and pharmaceutically acceptable salts thereof. Preferred NRIs include is desipramine and 1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol, particularly pure R and S enantiomers of 1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol. The dimethyl amine derivatives may be synthesized as described, for example, in US-A-4,535,186, the disclosure of which is incorporated herein by reference in its entirety. The piperazine derivatives may be synthesized as described, for example, in US-A-4,826,844, the disclosure of which is incorporated herein by reference in its entirety.

**[0037]** In another embodiment, a dual acting compound with norepinephrine reuptake inhibitor (NRI) activity and serotonin reuptake inhibitor (SRI) activity plays an important role in maintaining normal body temperature. A SRI compound alone did not abate hot flush. Surprisingly, an NRI compound, desipramine, when co-

administered with a SRI compound resulted in significantly enhanced abatement of naloxone-induced hot flush. Accordingly, the efficacy of norepinephrine reuptake inhibitor was significantly increased in the presence of serotonin reuptake inhibitor.

**[0038]** In yet another embodiment, the invention is directed to methods for treating or preventing vasomotor symptoms in a subject in need thereof, comprising the step of:

administering to said subject a therapeutically effective amount of at least one dual NRI/SRI compound or pharmaceutically acceptable salt thereof,

wherein said amount is less than about 37.5 mg/day, preferably, less than about 30 mg/day, even more preferably, less than about 25 mg/day, yet even more preferably, less than about 20 mg/day, less than about 15 mg/day, less than about 10 mg/day, and less than about 5 mg/day. Surprisingly, these therapeutically effective amounts are lower than levels used in the prior art to achieve abatement of vasomotor symptoms.

**[0039]** Examples of dual NRI/SRI compounds are venlafaxine, O-desmethyl-venlafaxine (DVS-233 or ODV), milnacipran, duloxetine, and combinations and pharmaceutically acceptable salts thereof. Accordingly, any combination of the above mentioned NRI or SRI such as venlafaxine, duloxetine, or milnacipran or components that have dual NRI/SRI activity (dual acting compound) could be used to maintain normal thermoregulatory homeostasis without reported side effects.

**[0040]** In yet another embodiment, venlafaxine was able to alleviate an elevated naloxone-dependent hot flush induced by an adrenergic $\alpha_2$  receptor antagonist, atipamezole. The results indicated a possible mechanism for venlafaxine increasing norepinephrine signaling through the adrenergic $\alpha_2$  receptor.

**[0041]** The combination of an NRI and an SRI has several additional advantages over the use of SRI alone to treat vasomotor symptoms. SRI alone induces vomiting, nausea and sexual dysfunction (*Annals of Oncology*, 2000, 11:17-22). The combination of SRI and NRI activity will reduce the effective dose of SRI

and will result in reduction of SRI side effects along with faster onset of the drug action. For example, when an increasing dose of NRI and a 10 mg/kg dose of SRI were co-administered, hot flush was abated by 100% at a 3 mg/kg dose of desipramine (Figure 4) compared with the 10 mg/kg dose.

**[0042]** In yet other preferred embodiments, the invention is directed to methods wherein the composition further comprises a therapeutically effective amount of at least one adrenergic $\alpha_2$  receptor antagonist or a pharmaceutically acceptable salt thereof. In certain preferred embodiments, the norepinephrine reuptake inhibitor and the adrenergic $\alpha_2$  receptor antagonist are administered simultaneously or concurrently. In certain preferred embodiments, the adrenergic $\alpha_2$  receptor antagonist is selective for the adrenergic $\alpha_{2A}$  receptor, adrenergic $\alpha_{2B}$  receptor, adrenergic $\alpha_{2C}$  receptor, or adrenergic $\alpha_{2D}$  receptor.

**[0043]** Adrenergic $\alpha_2$  receptor antagonists are known to induce hot flush. Surprisingly, an adrenergic $\alpha_2$  receptor antagonist when co-administered with a NRI compound, resulted in hot flush abatement. In one embodiment, the abatement of a naloxone-induced flush was enhanced by more than 50% when a NRI was co-administered with an adrenergic $\alpha_2$  receptor antagonist. Thus, demonstrating that the efficacy of an NRI was potentiated when administered in combination with an adrenergic $\alpha_2$  receptor antagonist. The dose level may require adjustment according to the dose of adrenergic $\alpha_2$  receptor antagonist administered, in order to block side effects without altering the efficacy on hot flushes. One of ordinary skill in the art will know how to determine such doses without undue experimentation.

**[0044]** Examples of adrenergic $\alpha_2$  receptor antagonist include, but are not limited to, atipamezole; 2-[2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl]-4,4-dimethyl-1,3-(2H,4H)-isoquinolindione dihydrochloride (ARC 239 dihydrochloride); 2-[(4,5-dihydro-1H-imidazol-2-yl)methyl]-2,3-dihydro-1-methyl-1H-isoindole maleate (BRL 44408 maleate); BRL48962; BRL41992; SKF 104856; SKF 104078; MK912; 2-(2-ethyl-2,3-dihydro-2-benzofuranyl)-4,5-dihydro-1H-imidazole hydrochloride (efaroxan hydrochloride); 2-(1,4-benzodioxan-2-yl)-2-imidazoline hydrochloride (idazoxan

hydrochloride); 2-(1-ethyl-2-indazolyl)methyl-1,4-benzodioxan hydrochloride (imiloxan hydrochloride); 17 $\alpha$ -hydroxy-20 $\alpha$ -yohimban-16 $\beta$ -carboxylic acid, methyl ester hydrochloride (rauwolscine hydrochloride); (8 $\alpha$ R,12 $\alpha$ S,13 $\alpha$ S)-5,8,8 $\alpha$ ,9,10,11,12,12 $\alpha$ ,13,13 $\alpha$ -dehydro-3-methoxy-12-(ethylsulfonyl)-6H-isoquino[2,1- $\gamma$ ][1,6]naphthyridine hydrochloride (RS 79948 hydrochloride); 2-(2,3-dihydro-2-methoxy-1,4-benzodioxin-2-yl)-4,5-dihydro-1H-imidazole hydrochloride (RX 821002 hydrochloride); 8-[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one (spiroxatrine); 17 $\alpha$ -hydroxy-yohimban-16 $\alpha$ -carboxylic acid methyl ester hydrochloride (yohimbine hydrochloride); and combinations and pharmaceutically acceptable salts thereof. Several of these compounds are available from Tocris Cookson Inc., Ellisville, MO.

**[0045]** In certain preferred embodiments, the adrenergic $\alpha_2$  receptor antagonist is selective for the adrenergic $\alpha_{2A}$  receptor, adrenergic $\alpha_{2B}$  receptor, adrenergic $\alpha_{2C}$  receptor, or adrenergic $\alpha_{2D}$  receptor. BRL44408 and BRL48962 are known to be selective adrenergic $\alpha_{2A}$  receptor antagonists. Imiloxan is a known selective adrenergic $\alpha_{2A}$  receptor antagonist. Rauwolscine and MK912 are known selective adrenergic $\alpha_{2A}$  receptor antagonists.

**[0046]** In other embodiments, the invention is directed to pharmaceutical compositions, comprising:

- a. at least one norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof;
- b. at least one serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof; and
- c. at least one pharmaceutically acceptable carrier.

Generally, the norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof will be present at a level of from about 0.1%, by weight, to about 90% by weight, based on the total weight of the pharmaceutical composition, and serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof will be present at a level of from about 0.1%, by weight, to about 90% by weight, based on the total weight of the pharmaceutical composition. Preferably, the norepinephrine reuptake

inhibitor or a pharmaceutically acceptable salt thereof will be present at a level of at least about 1%, by weight, and the serotonin reuptake inhibitor will be present at a level of at least about 1%, based on the total weight of the pharmaceutical composition. More preferably, the norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof will be present at a level of at least about 5%, by weight, and the serotonin reuptake inhibitor will be present at a level of at least about 5%, based on the total weight of the pharmaceutical composition. Even more preferably, the norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof will be present at a level of at least about 10%, by weight, and the serotonin reuptake inhibitor will be present at a level of at least about 10%, based on the total weight of the pharmaceutical composition. Yet even more preferably, the norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof will be present at a level of at least about 25%, by weight, and the serotonin reuptake inhibitor will be present at a level of at least about 25%, based on the total weight of the pharmaceutical composition.

[0047] In other embodiments, the invention is directed to pharmaceutical compositions, comprising:

- a. at least one norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof;
- b. at least one adrenergic $\alpha_2$  receptor antagonist or a pharmaceutically acceptable salt thereof; and
- c. at least one pharmaceutically acceptable carrier.

Generally, the norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof will be present at a level of from about 0.1%, by weight, to about 90% by weight, based on the total weight of the pharmaceutical composition, and adrenergic $\alpha_2$  receptor antagonist or a pharmaceutically acceptable salt thereof will be present at a level of from about 0.1%, by weight, to about 90% by weight, based on the total weight of the pharmaceutical composition. Preferably, the norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof will be present at a level of at least about 1%, by weight, and the adrenergic $\alpha_2$  receptor antagonist will be present at a level of at least about 1%, based on the total weight of

the pharmaceutical composition. More preferably, the norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof will be present at a level of at least about 5%, by weight, and the adrenergic $\alpha_2$  receptor antagonist will be present at a level of at least about 5%, based on the total weight of the pharmaceutical composition. Even more preferably, the norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof will be present at a level of at least about 10%, by weight, and the adrenergic $\alpha_2$  receptor antagonist will be present at a level of at least about 10%, based on the total weight of the pharmaceutical composition. Yet even more preferably, the norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof will be present at a level of at least about 25%, by weight, and the adrenergic $\alpha_2$  receptor antagonist will be present at a level of at least about 25%, based on the total weight of the pharmaceutical composition.

[0048] In certain preferred embodiments, the norepinephrine reuptake inhibitor and adrenergic $\alpha_2$  receptor antagonist are a single compound. In other preferred embodiments, norepinephrine reuptake inhibitor and adrenergic $\alpha_2$  receptor antagonist are a combination of two or more compounds.

[0049] Such compositions are prepared in accordance with acceptable pharmaceutical procedures, such as described in *Remingtons Pharmaceutical Sciences*, 17th edition, ed. Alfonso R. Gennaro, Mack Publishing Company, Easton, PA (1985). Pharmaceutically acceptable carriers are those that are compatible with the other ingredients in the formulation and biologically acceptable.

[0050] The compounds of this invention may be administered orally or parenterally, neat or in combination with conventional pharmaceutical carriers. Applicable solid carriers can include one or more substances that may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a finely divided solid that is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and

compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

**[0051]** Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups, and elixirs. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers, or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, *e.g.* cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols *e.g.* glycols) and their derivatives, and oils (*e.g.* fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

**[0052]** Liquid pharmaceutical compositions, which are sterile solutions or suspensions, can be administered by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.

**[0053]** Preferably the pharmaceutical composition is in unit dosage form, *e.g.* as tablets, capsules, powders, solutions, suspensions, emulsions, granules, or suppositories. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a

capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

**[0054]** The following definitions are provided for the full understanding of terms and abbreviations used in this specification.

**[0055]** As used herein and in the appended claims, the singular forms "a," "an," and "the" include the plural reference unless the context clearly indicates otherwise. Thus, for example, a reference to "an antagonist" includes a plurality of such antagonists, and a reference to "a compound" is a reference to one or more compounds and equivalents thereof known to those skilled in the art, and so forth.

**[0056]** The phrases "vasomotor symptoms," "vasomotor instability symptoms" and "vasomotor disturbances" include, but are not limited to, hot flushes (flashes), insomnia, sleep disturbances, mood disorders, irritability, excessive perspiration, night sweats, fatigue, and the like, caused by, *inter alia*, thermoregulatory dysfunction.

**[0057]** The term "hot flush" is an art-recognized term that refers to an episodic disturbance in body temperature typically consisting of a sudden skin flushing, usually accompanied by perspiration in a subject. The term "hot flush" may be used interchangeably with the terms vasomotor symptoms, vasomotor instability, vasomotor dysfunction, night sweats, vasomotor disturbances, and hot flash.

**[0058]** The phrase "a compound having norepinephrine reuptake inhibitor activity," as used herein, refers to a compound that alters the level of norepinephrine (NE) by inhibiting the uptake of NE through neurons of the central and/or peripheral nervous system and/or the peripheral system and that has a selectivity ratio of SERT:NET activity, as measured by the EC<sub>50</sub> value or by % specific bound NE uptake for the human transporter, of at least about 1:1. Preferably, the selectivity ratio of SERT:NET does not exceed about 1000:1. Preferably, the selectivity ratio of SERT:NET is greater than about 2:1. More preferably, the selectivity ratio of SERT:NET is greater than about 5:1. Even more preferably, the selectivity ratio of

SERT:NET is greater than about 10:1. In alternatively preferred embodiments, the ratio of SERT:NET is greater than about 10:1 to less than about 500:1, preferably less than about 300:1.

**[0059]** The phrase "a compound having serotonin reuptake inhibitor activity," as used herein, refers to a compound that increases the level of serotonin by inhibiting the uptake of serotonin through neurons of the central and/or peripheral nervous system and/or the peripheral system.

**[0060]** The phrase "a compound having dual NRI/SRI activity," as used herein, refers to a single compound having dual activity as a serotonin reuptake inhibitor and as a norepinephrine reuptake inhibitor. As used herein, a compound having a dual activity is a dual acting compound.

**[0061]** The abbreviations in the specification correspond to units of measure, techniques, properties, or compounds as follows: "min" means minutes, "h" means hour(s), "μL" means microliter(s), "mL" means milliliter(s), "mM" means millimolar, "M" means molar, "mmole" means millimole(s), "cm" means centimeters, "SEM" means standard error of the mean and "IU" means International Units. "Δ°C" and Δ TST mean change in tail skin temperature normalized for 15 minutes baseline TST prior to naloxone-induced flush. "ED<sub>50</sub> value" means dose which results in 50% alleviation of the observed condition or effect (50% mean maximum endpoint).

"Tail skin temperature" is abbreviated TST.

"Norepinephrine transporter" is abbreviated NET.

"Human norepinephrine transporter" is abbreviated hNET.

"Serotonin transporter" is abbreviated SERT.

"Human serotonin transporter" is abbreviated hSERT.

"Norepinephrine reuptake inhibitor" is abbreviated NRI.

"Selective norepinephrine reuptake inhibitor" is abbreviated SNRI.

"Serotonin reuptake inhibitor" is abbreviated SRI.

"Selective serotonin reuptake inhibitor" is abbreviated SSRI.

"Norepinephrine" is abbreviated NE.

"Serotonin is abbreviated 5-HT.

"Subcutaneous" is abbreviated sc.

"Intraperitoneal" is abbreviated ip.

"Oral" is abbreviated po.

**[0062]** In the context of this disclosure, a number of terms shall be utilized. The term "treatment" as used herein includes preventative (e.g., prophylactic), curative or palliative treatment and "treating" as used herein also includes preventative, curative and palliative treatment.

**[0063]** A "therapeutically effective amount" refers to an amount effective, at dosages, and for periods of time necessary, to achieve the desired result. In particular, "therapeutically effective amount" refers to the amount of compound or composition of compounds that would increase norepinephrine levels to compensate in part or total for the lack of steroid availability in subjects subject afflicted with a vasomotor symptom. Varying hormone levels will influence the amount of compound required in the present invention. For example, the pre-menopausal state may require a lower level of compound due to higher hormone levels than the peri-menopausal state.

**[0064]** It will be appreciated that the therapeutically effective amount of components of the present invention will vary from patient to patient not only with the particular compound, component or composition selected, the route of administration, and the ability of the components (alone or in combination with one or more combination drugs) to elicit a desired response in the individual, but also with factors such as the disease state or severity of the condition to be alleviated, hormone levels, age, sex, weight of the individual, the state of being of the patient, and the severity of the pathological condition being treated, concurrent medication or special diets then being followed by the particular patient, and other factors which those skilled in the art will recognize, with the appropriate dosage ultimately being at the discretion of the attendant physician. Dosage regimens may be adjusted to provide the improved therapeutic response. A therapeutically effective amount is also one in which any toxic or detrimental effects of the components are outweighed

by the therapeutically beneficial effects.

[0065] Preferably, the compounds of the present invention are administered at a dosage and for a time such that the number of hot flushes is reduced as compared to the number of hot flushes prior to the start of treatment. Such treatment can also be beneficial to reduce the overall severity or intensity distribution of any hot flushes still experienced, as compared to the severity of hot flushes prior to the start of the treatment.

[0066] For example, for a patient who experiences any number of hot flushes, compounds having NRI activity or combination of compounds SRI and NRI activities may be administered, preferably, at a dosage of from about 0.1 mg/day to about 200 mg/day, more preferably from about 1 mg/day to about 100 mg/day and most preferably from about 1 mg/day to 50 mg/day for a time sufficient to reduce and/or substantially eliminate the number and/or severity of hot flushes or such that hot flushes.

[0067] Furthermore, a compound having an NRI activity can be co-administered with a compound having adrenergic $\alpha_2$  receptor antagonist activity preferably at dosage of about 0.1 mg/day to about 300 mg/day, more preferably from about 1 mg/day to 200 mg/day, and most preferably from about 1 mg/day to 100 mg/day for a time sufficient to reduce and/or substantially eliminate the number and/or severity of hot flushes or such that hot flushes.

[0068] The terms "component," "composition of compounds," "compound," "drug," or "pharmacologically active agent" or "active agent" or "medicament" are used interchangeably herein to refer to a compound or compounds or composition of matter which, when administered to a subject (human or animal) induces a desired pharmacological and/or physiologic effect by local and/or systemic action. The component herein may contain NRI activity alone or combination of NRI and SRI activity. The component of the present invention may contain substantially no SRI activity or exhibit NRI activity essentially in the absence of SRI activity. Furthermore, the compound of the present invention may contain combination of NRI activity and

in combination with adrenergic  $\alpha_2$  receptor antagonist activity.

[0069] The terms "component", "drug" or "pharmacologically active agent" or "active agent" or "medicament" are used interchangeably herein to refer to a compound or compounds or composition of matter which, when administered to an organism (human or animal) induces a desired pharmacologic and/or physiologic effect by local and/or systemic action. The component herein may contain norepinephrine reuptake inhibiting activity or combined serotonin reuptake inhibiting activity and the norepinephrine reuptake inhibiting activity. Furthermore, the component herein may contain combined norepinephrine reuptake inhibiting activity and the adrenergic  $\alpha_2$  receptor antagonist activity.

[0070] The term "modulation" refers to the capacity to either enhance or inhibit a functional property of a biological activity or process, for example, receptor binding or signaling activity. Such enhancement or inhibition may be contingent on the occurrence of a specific event, such as activation of a signal transduction pathway and/or may be manifest only in particular cell types. The modulator is intended to comprise any compound, *e.g.*, antibody, small molecule, peptide, oligopeptide, polypeptide, or protein, preferably small molecule, or peptide.

[0071] As used herein, the term "inhibitor" refers to any agent that inhibits, suppresses, represses, or decreases a specific activity, such as serotonin reuptake activity or the norepinephrine reuptake activity.

[0072] The term "inhibitor" is intended to comprise any compound, *e.g.*, antibody, small molecule, peptide, oligopeptide, polypeptide, or protein, preferably small molecule or peptide, that exhibits a partial, complete, competitive and/or inhibitory effect on mammalian, preferably the human norepinephrine reuptake or both serotonin reuptake and the norepinephrine reuptake, thus diminishing or blocking, preferably diminishing, some or all of the biological effects of endogenous norepinephrine reuptake or of both serotonin reuptake and the norepinephrine reuptake.

[0073] Within the present invention, the NRIs, SRIs, NRI/SRIs, and adrenergic $\alpha_2$  receptor antagonists may be prepared in the form of pharmaceutically acceptable salts. As used herein, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids, including inorganic salts, and organic salts. Suitable non-organic salts include inorganic and organic acids such as acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, malic, maleic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic and the like. Particularly preferred are hydrochloric, hydrobromic, phosphoric, and sulfuric acids, and most preferably is the hydrochloride salt.

[0074] "Administering," as used herein, means either directly administering a compound or composition of the present invention, or administering a prodrug, derivative or analog which will form an equivalent amount of the active compound or substance within the body.

[0075] The present invention includes prodrugs of NRIs, SRIs, NRI/SRIs, and adrenergic $\alpha_2$  receptor antagonists. "Prodrug," as used herein, means a compound which is convertible *in vivo* by metabolic means (*e.g.* by hydrolysis) to a NRIs, SRIs, NRI/SRIs, and adrenergic $\alpha_2$  receptor antagonists. Various forms of prodrugs are known in the art, for example, as discussed in Bundgaard, (ed.), *Design of Prodrugs*, Elsevier (1985); Widder, et al. (ed.), *Methods in Enzymology*, vol. 4, Academic Press (1985); Krogsgaard-Larsen, et al., (ed). "Design and Application of Prodrugs, Textbook of Drug Design and Development, Chapter 5, 113-191 (1991), Bundgaard, et al., *Journal of Drug Deliver Reviews*, 1992, 8:1-38, Bundgaard, *J. of Pharmaceutical Sciences*, 1988, 77:285 *et seq.*; and Higuchi and Stella (eds.) *Prodrugs as Novel Drug Delivery Systems*, American Chemical Society (1975).

[0076] Within the present invention, NRIs, SRIs, NRI/SRIs, and adrenergic $\alpha_2$  receptor antagonists may be prepared in the form of pharmaceutically acceptable salts, including salts of organic acids and minerals. The acid addition

salts of NRIs are preferred.

[0077] Further, the compounds of the present invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purpose of the present invention.

[0078] A pharmaceutical composition for use in accordance with the present invention comprises a norepinephrine reuptake inhibitor, or a serotonin reuptake inhibitor and norepinephrine reuptake inhibitor, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier. The composition may comprise one or more norepinephrine reuptake inhibitor(s), or one or more each of serotonin reuptake inhibitor(s) and norepinephrine reuptake inhibitor(s) as active ingredient(s), together with one or more pharmaceutically acceptable carrier(s).

[0079] A pharmaceutical composition for use in accordance with the present invention comprises a norepinephrine reuptake inhibitor, or an adrenergic $\alpha_2$  receptor antagonist and norepinephrine reuptake inhibitor, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier. The composition may comprise one or more norepinephrine reuptake inhibitor(s), or one or more each of adrenergic $\alpha_2$  receptor antagonist(s) and norepinephrine reuptake inhibitor(s) as active ingredient(s), together with one or more pharmaceutically acceptable carrier(s).

[0080] Some of the compounds of the present invention may contain chiral centers and such compounds may exist in the form of stereoisomers (*i.e.* enantiomers). The present invention includes all such stereoisomers and any mixtures thereof including racemic mixtures. Racemic mixtures of the stereoisomers as well as the substantially pure stereoisomers are within the scope of the invention. The term "substantially pure," as used herein, refers to at least about 90 mole %, more preferably at least about 95 mole %, and most preferably at least about 98 mole % of the desired stereoisomer is present relative to other possible

stereoisomers. Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including high performance liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by methods described herein. See, for example, Jacques, *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen, S.H., *et al.*, *Tetrahedron*, 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds*, (McGraw-Hill, NY, 1962); Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions*, p. 268 (E.L. Eliel, Ed., University of Notre Dame Press, Notre Dame, IN 1972).

**[0081]** A pharmaceutical for use in accordance with the present invention comprises NRI alone, NRI/SRI or NRI in combination with at least one adrenergic<sub>α2</sub> receptor antagonist, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier. The composition may comprise one or more NRI(s), one or more each of NRI and SRI, one or more of NRI/SRI(s) or one or more of each of NRI and adrenergic<sub>α2</sub> receptor antagonist as active ingredient(s), together with one or more pharmaceutically acceptable carrier(s).

**[0082]** The term "combination therapy" refers to the administration of two or more therapeutic agents or compounds to treat a therapeutic condition or disorder described in the present disclosure, for example hot flush, sweating, thermoregulatory-related condition or disorder, or other. Such administration includes co-administration of these therapeutic agents or compounds in a simultaneous manner, such as in a single compound having NRI/adrenergic<sub>α2</sub> receptor antagonist activity or in multiple, separate compounds for each NRI, SRI or adrenergic<sub>α2</sub> receptor antagonist activities. In addition, such administration also includes use of each type of therapeutic agent in a concurrent manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

**[0083]** The route of administration may be any route, which effectively transports the active norepinephrine reuptake inhibitor(s) or serotonin reuptake inhibitor(s) and norepinephrine reuptake inhibitor(s) to the appropriate or desired site

of action, such as oral, nasal, pulmonary, transdermal, such as passive or iontophoretic delivery, or parenteral, *e.g.* rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment. Furthermore, the administration of norepinephrine reuptake inhibitor(s) and serotonin reuptake inhibitor(s) may be concurrent or simultaneous.

**[0084]** The term "subject" or "patient" refers to an animal including the human species that is treatable with the compositions, and/or methods of the present invention. The term "subject" or "subjects" is intended to refer to both the male and female gender unless one gender is specifically indicated. Accordingly, the term "patient" comprises any mammal which may benefit from treatment or prevention of vasomotor disturbances, such as a human, especially if the mammal is female, either in the pre-menopausal, peri-menopausal, or post-menopausal period. Furthermore, the term patient comprises female animals including humans and, among humans, not only women of advanced age who have passed through menopause but also women who have undergone hysterectomy or for some other reason have suppressed estrogen production, such as those who have undergone long-term administration of corticosteroids, suffer from Cushing's syndrome or have gonadal dysgenesis. However, the term "patient" is not intended to be limited to a woman.

**[0085]** The terms "premature menopause" or "artificial menopause" refer to ovarian failure of unknown cause that may occur before age 40. It may be associated with smoking, living at high altitude, or poor nutritional status. Artificial menopause may result from oophorectomy, chemotherapy, radiation of the pelvis, or any process that impairs ovarian blood supply.

**[0086]** The term "pre-menopausal" means before the menopause, the term "peri-menopausal" means during the menopause and the term "post-menopausal" means after the menopause. "Ovariectomy" means removal of an ovary or ovaries and can be effected according to Merchenthaler *et al.*, *Maturitas*, 1998, 30(3): 307-316.

[0087] "Side effect" refers to a consequence other than the one(s) for which an agent or measure is used, as the adverse effects produced by a drug, especially on a tissue or organ system other than the one sought to be benefited by its administration. In the case, for example, of high doses of NRIs or NRI/SRI compounds alone, the term "side effect" may refer to such conditions as, for example, vomiting, nausea, sweating, and flushes (Janowsky, *et al.*, *Journal of Clinical Psychiatry*, 1984, 45(10 Pt 2): 3-9).

## EXAMPLES

[0088] The present invention is further defined in the following Examples, in which all parts and percentages are by weight and degrees are Celsius, unless otherwise stated. It should be understood that these examples, while indicating preferred embodiments of the invention, are given by way of illustration only. From the above discussion and these examples, one skilled in the art can ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

## GENERAL METHODS

[0089] Reagents: Venlafaxine and O-Desmethyl-venlafaxine (DVS-233 or ODV) may be prepared as described in US-A-4,535,186. Desipramine can be prepared as described in US-A-3,454,554. Reboxetine can be prepared as described in U.S. Patent Publication No. 2002/0107249. 1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl] cyclohexanol (racemic), *R*-1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl] cyclohexanol, *S*-1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl] cyclohexanol, 1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol, 1-[1-(3-chloro-phenyl)-2-piperazin-1-yl-ethyl]-cyclohexanol and 1-[2-(dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol may be prepared as described in US-A-4,826,844 (piperazine derivatives) or US-A-4,535,186 (dimethylamino derivatives). The following reagents were purchased commercially: fluoxetine (Sigma, St. Louis,

MO), morphine alkaloid pellets (Murty Pharmaceuticals, Lexington, KY), atipamezole (Pfizer, NY, NY), ketamine (Phoenix Pharmaceuticals, Belmont, CA), and naloxone (Research Biochemicals International, St. Louis, MO).

**[0090]    Dosing:** All doses were prepared based on mg/kg. Compounds were dissolved in sterile water, 0.25% Tween/methylcellulose or 2.0% Tween/methylcellulose and injected subcutaneously (sc) or intraperitoneally (ip), and used at the following dosages: venlafaxine (1, 8, 10, 20, and 40 mg/kg), ODV (1, 10, 30 and 60 mg/kg), fluoxetine (10, 20, 60 mg/kg), desipramine (0.01, 1.0, 10, and 30 mg/kg), reboxetine (0.01, 1.0, 10, 30 and 60 mg/kg), R-1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl] cyclohexanol (30 mg/kg, ip), R-1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl] cyclohexanol, (30 mg/kg, ip), S-1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl] cyclohexanol, (30 mg/kg, ip), 1-[1-(3-chloro-phenyl)-2-piperazin-1-yl-ethyl]-cyclohexanol. (30 mg/kg, ip), 1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol (30 mg/kg, sc), 1-[2-(dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol (30 mg/kg, sc), and atipamezole (1 mg/kg). Ketamine (Ketaject, Phoenix Pharmaceuticals, Belmont, CA) was injected intramuscularly in the hind limb at a dosage (40mg/kg) that was determined to be mildly sedative but did not cause a change in tail skin temperature.

**[0091]    Animals:** Ovariectomized Sprague-Dawley rats (180-220g) were obtained from a commercial vendor (Taconic, Germantown, NY) and individually housed under 12 hours light/dark cycle in a room maintained at 25°C. Animals were provided with standard rat chow and water *ad libitum*.

**[0092]    Morphine-dependent model:** Ovariectomized rats were injected once daily for 8-9 days with vehicle to minimize stress responses and then administered compound(s) on test day. On day 4 of dosing, morphine dependence was induced by sc implantation of two slow-release morphine pellets (75 mg/pellet) in the dorsal scapular region. This model is based upon an established morphine-dependent naloxone-induced flush paradigm that is reversible by estrogen treatment (Katovich *et al.*, *Proceedings of the Society for Experimental Biology & Medicine*, **1990**, 193(2): 129-35). Four to six days after implantation, morphine withdrawal was induced with

an opioid antagonist (naloxone) that causes a transient increase in TST. In a typical experiment, rats were administered their final dose of test compound 40 to 60 minutes prior to naloxone injection. Rats were mildly sedated with ketamine and a thermistor connected to a MacLab data acquisition system was taped to the base of the tail. Tail skin temperature was then monitored continuously for 35 minutes to establish a baseline temperature. Naloxone was subsequently administered and TST was measured for an additional 35 to 60 minutes (total recording time 70 to 95 minutes).

**[0093] Telemetry model:** This model has been modified from a previously reported protocol describing estrogen regulation of diurnal TST patterns (Berendsen *et al.*, 2001). Over a 24-hour period, intact cycling rats decrease TST during the active (dark) phase and TST remains elevated during the inactive (light) phase. In OVX rats, TST is elevated over the entire 24-hour period, thus the usual decrease in TST during the active (dark) phase is lost, thus, a compound's ability to restore this lowering of TST during the active phase was examined. A temperature and physical activity transmitter (PhysioTel TA10TA-F40, Data Sciences International) was implanted subcutaneously in the dorsal scapular region and the tip of the temperature probe was tunneled subcutaneously 2.5 cm beyond the base of the tail. After a 7-day recovery period, TST readings were continuously recorded for the remainder of the study. Tail skin temperature readings were collected from each animal every 5 minutes with values obtained over a 10 second sampling period. The day before test day, an average baseline TST value was calculated for each animal by averaging temperature readings recorded during the 12 hours active (dark) phase. In these studies, animals were dosed approximately 1 hour prior to the onset of dark cycle.

**[0094] Statistical analysis:** To analyze changes in TST induced by naloxone in morphine-dependent rats, all data were analyzed using a two factor repeated measure ANOVA for "treatment" and "time." The model was fit to test whether there were significant differences in the responses between treatment groups. Naloxone administration is designated as time zero and data is then analyzed at 5 minute intervals. The first three readings were averaged and used as baseline TST scores.

All data were analyzed as  $\Delta$ TST (TST for each time point – baseline). Multiple comparisons (LSD p-values) among the treatment groups at each time point were used for the analysis. Efficacy of hot flush abatement was determined by evaluating statistical differences at the peak response time of 15 minutes post-naloxone, when the maximal change in TST is observed. A customized SAS-excel (SAS Institute, Cary, NC) application was used applying a four parameter logistic model to determine  $ED_{50}$  values. A logistic dose transformation was performed on  $\Delta$ TST. Maximum flush ( $\Delta$ TST at 15 minutes post-naloxone) was used in the analysis and the minimum was locked at zero. The  $ED_{50}$  value is reported as the dose of test compound that abates 50% of the naloxone- induced flush. Statisticians in the Biometrics Department (Wyeth Research, Collegeville, PA) developed a customized JMP application.

**[0095]** Evaluation of a compound's ability to restore normal lowering of TST in the telemetry model was analyzed using hourly TST values calculated for each animal by averaging the 12 temperature readings obtained every 5 minutes over that recording time. To analyze  $\Delta$ TST in the telemetry model, a two factors repeated measure ANOVA was performed. The model used for analysis was  $\Delta$ TST = GRP (group) + HR (hours) + GRP\*HR + BASELINE. Thus, the reported least squares means are the expected mean values as if both groups had the same baseline value. Post-hoc tests of hourly GRP\*HR samples are t-tests of the difference between groups for each hour. To be conservative, a result was not considered significant unless the p-value was < 0.025. All analyses were performed using SAS PROC MIXED (SAS, Carey, NC).

#### **EXAMPLE 1**

##### **Effect of NRIs in Alleviating Vasomotor Instability in Pre-clinical Models of Vasomotor Instability**

**[0096]** Method used as described in the general method section under morphine-dependent rat model with the following exceptions: Rats were injected subcutaneously with vehicle (sterile H<sub>2</sub>O) or desipramine that may be prepared as described in U.S. Patent Publication No. 2002/0107249, dissolved in sterile H<sub>2</sub>O and administered at 0.1, 1.0, 10 and 30 mg/kg 1 hour prior to naloxone (**Figure 3A**). At

maximal flush (15 minutes post-naloxone;  $\Delta^{\circ}\text{C}$ , Mean + SEM) desipramine dose-dependently abates the naloxone-induced flush.

[0097] Rats were injected subcutaneously with vehicle (sterile  $\text{H}_2\text{O}$ ) or desipramine dissolved in sterile  $\text{H}_2\text{O}$  and administered at 10 mg/kg) (Figure 3B). Changes in TST ( $\Delta^{\circ}\text{C}$ , Mean + SEM) over time in the telemetry model of OVX-induced thermodyregulation demonstrate that desipramine significantly decreases TST over the entire length of the active phase (Figure 3B). An analysis of results indicated that desipramine at doses of 10 mg/kg and 30 mg/kg was able to abate 90.4% and 96.7%, respectively, of naloxone-induced hot flush in a rat model of vasomotor instability. In addition, NRI compounds can be used to restore normal thermoregulation as depicted in the OVX-induced thermoregulatory dysfunction telemetry model.

[0098] Method used as described in the general method section under morphine-dependent rat model with the following exceptions: Rats were injected subcutaneously with vehicle (sterile  $\text{H}_2\text{O}$ ) or reboxetine that may be prepared as described in US-A-4,229,449, dissolved in sterile  $\text{H}_2\text{O}$  and administered at 0.01, 1.0, 10, 30 and 60 mg/kg) 1 hour prior to naloxone (Figure 3C). At maximal flush (15 minutes post-naloxone;  $\Delta^{\circ}\text{C}$ , Mean + SEM) reboxetine dose-dependently abates the naloxone-induced flush.

[0099] Method as described in the general method section under morphine-dependent rat model with the following exceptions: Rats were injected subcutaneously with vehicle (sterile  $\text{H}_2\text{O}$ ), reboxetine (which was prepared as described in U.S. Patent Publication No. 2002/0107249 A1, dissolved in sterile  $\text{H}_2\text{O}$  and administered at 0.01, 1.0, 10, 30 60 mg/kg) or 1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperaziny)ethyl]cyclohexanol (which was prepared as described in US-A-4,826,844, dissolved in sterile  $\text{H}_2\text{O}$  and administered at 7.5, 15, 30 mg/kg). Changes in TST ( $\Delta^{\circ}\text{C}$ , Mean) over time in the morphine-dependent rat model depict that both reboxetine (Figure 3D) and 1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperaziny)ethyl]cyclohexanol (Figure 3E) dose-dependently abate the naloxone-

induced flush. These results indicate that increasing NE levels with NRIs can alleviate vasomotor instability.

[0100] Method used as described in the general method section under morphine-dependent rat model with the following exceptions: Rats were injected intraperitoneally with vehicle (0.25% Tween/methylcellulose) or 1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol (WY-781), and 1-[2-(dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol (WY-867), prepared in accordance with US-A-4,535,186, dissolved in 0.25% Tween/methylcellulose and administered at 30 mg/kg) 1 hour prior to naloxone (Figure 3F). At maximal flush (15 minutes post-naloxone;  $\Delta^{\circ}\text{C}$ , Mean + SEM) both compounds abated the naloxone-induced flush in the MD model.

## **EXAMPLE 2**

### **Effect of a Combination of NRI and SRI on Alleviation of Vasomotor Instability**

[0101] Method are described in the general method section under morphine-dependent rat model with the following exceptions: Rats were injected subcutaneously with vehicle sterile  $\text{H}_2\text{O}$ ), desipramine, (which was prepared as described in US-A-3,454,554, dissolved in sterile  $\text{H}_2\text{O}$  and administered at 0.1, 1.0, 10 mg/kg) or fluoxetine (Sigma, dissolved in sterile  $\text{H}_2\text{O}$  at 10, 30, 60 mg/kg) or combination of fluoxetine administered at 10 mg/kg and increasing doses of desipramine listed above 1 hour prior to naloxone.

[0102] At maximal hot flush (15 minutes post-naloxone;  $\Delta^{\circ}\text{C}$ , Mean + SEM) desipramine dose-dependently abates the naloxone-induced flush in the MD model but results in a shallow slope of the estimated line (solid line, Figure 4). The shallow slope of the estimated line is typical of compounds that have multiple site interactions. Therefore, a dose of fluoxetine that did not abate the naloxone-induced flush was used to determine if there was an interaction between the NE and 5-HT systems. In the presence of 10 mg/kg fluoxetine, the slope of the estimated line for the desipramine dose response curve shifted to a natural sigmoidal curve indicative of a single site action. These data indicate that in the presence of saturating

concentrations of fluoxetine, desipramine is acting solely through the NE system. Although the ED<sub>50</sub> value for desipramine (1 mg/kg) did not change in the presence of fluoxetine, the maximally effective dose was shifted to the left. The results indicated that an NRI compound (desipramine, 10 mg/kg) abated a naloxone-induced hot flush and was significantly enhanced when the serotonin reuptake inhibitor (SRI), fluoxetine (10 mg/kg) was co-administered. Hence, the co-administration of a NRI and SRI compound (e.g. desipramine + fluoxetine) was more efficacious for treating hot flush.

### **EXAMPLE 3**

#### **Effect of Compounds with Dual NRI/SRI Activity on Alleviating Vasomotor Instability**

[0103] Method as described in the general method section under morphine-dependent rat model with the following exceptions: Rats were injected subcutaneously with vehicle (sterile H<sub>2</sub>O), venlafaxine (dissolved in sterile H<sub>2</sub>O and administered at 1.0, 10, 20, 40 mg/kg) or ), DVS-233 (dissolved in sterile H<sub>2</sub>O and administered at 1.0, 10, 30, 60 mg/kg) 1 hour prior to naloxone. Venlafaxine and DVS-233 were synthesized as described in US-A-4,535,186. At maximal flush (15 minutes post-naloxone; Δ°C, Mean + SEM) venlafaxine dose-dependently (ED<sub>50</sub> value= 15 + 7 mg/kg) abates the naloxone-induced flush (Figure 5A). At maximal flush (15 minutes post-naloxone; Δ°C, Mean + SEM) DVS-233 dose-dependently ED<sub>50</sub> value= 30 + 3 mg/kg) abates the naloxone-induced flush (Figure 5B).

[0104] Method of Figures 5C and 5D were as described in the general method section under telemetry model. Rats were injected subcutaneously with vehicle (sterile H<sub>2</sub>O), venlafaxine (dissolved in sterile H<sub>2</sub>O and administered at 15 mg/kg) or DVS-233 (dissolved in sterile H<sub>2</sub>O and administered at 60 mg/kg). Changes in TST (Δ°C, Mean + SEM) over time in the telemetry model demonstrated that venlafaxine significantly and transiently decreased TST during the active phase (Figure 5C). Changes in TST (Δ°C, Mean + SEM) over time in the telemetry model of demonstrated that DVS-233 significantly and transiently decreases TST during the active phase (Figure 5D). The results indicated that venlafaxine and DVS-233, dual acting SRI/NRI, effectively alleviated vasomotor instability. The results

indicated that dual acting compounds alleviate vasomotor instability by modulating the NE system via the NRI component.

**[0105]** Method as described in the general method section under morphine-dependent rat model with the following exceptions: Rats were injected subcutaneously with vehicle (sterile H<sub>2</sub>O), *R*-enantiomer of venlafaxine (*R*-venlafaxine, which was synthesized as described in US-A-4,535,186, dissolved in sterile H<sub>2</sub>O and administered at 0.3, 1.0, 10, 30 mg/kg), *S*-enantiomer of venlafaxine (*S*-venlafaxine, which was synthesized as described in US-A-4,535,186, dissolved in sterile H<sub>2</sub>O and administered at 1.0, 10, 30, 60 mg/kg), *R*-enantiomer of O-desmethylvenlafaxine (*R*-ODV, which was synthesized as described in US-A-4,535,186, dissolved in sterile H<sub>2</sub>O and administered at 1.0, 10, 30, 60 mg/kg), *S*-enantiomer of ODV (*S*-ODV, which was synthesized as described in US-A-4,535,186, dissolved in sterile H<sub>2</sub>O and administered at 1.0, 10, 30, 60 mg/kg), or paroxetine (which was synthesized as described in US-A-4,535,186, dissolved in sterile H<sub>2</sub>O and administered at 0.5, 5.0, 15, 30 mg/kg) 1 hour prior to naloxone administration. At maximal flush (15 minutes post-naloxone; Δ°C, Mean + SEM), *R*-venlafaxine dose-dependently (ED<sub>50</sub> value= 8.3+3 mg/kg) abates the naloxone-induced flush (**Figure 5E**). At maximal flush (15 min post-naloxone; Δ°C, Mean + SEM) *S*-venlafaxine dose-dependently (ED<sub>50</sub> value= 10.9+3 mg/kg) abates the naloxone-induced flush (**Figure 5F**). At maximal flush (15 minutes post-naloxone; Δ°C, Mean + SEM) *R*-ODV dose-dependently (ED<sub>50</sub> value= 14.4+13 mg/kg) abates the naloxone-induced flush (**Figure 5G**). At maximal flush (15 minutes post-naloxone; Δ°C, Mean + SEM) *S*-ODV dose-dependently (ED<sub>50</sub> value= 13.3+8 mg/kg) abates the naloxone-induced flush (**Figure 5H**). At maximal flush (15 minutes post-naloxone; Δ°C, Mean + SEM) paroxetine dose-dependently (ED<sub>50</sub> value= 22.3+11 mg/kg) abates the naloxone-induced flush (**Figure 5J**). The doses used for *R*-venlafaxine, *S*-venlafaxine, *R*-ODV, *S*-ODV and paroxetine were chosen based on their activity on the NE system or NE transporter system. The results indicate that *R*-venlafaxine, *S*-venlafaxine, *R*-ODV, *S*-ODV and paroxetine that all have dual SRI/NRI activity effectively alleviate hot flush. The results indicate that compounds with dual activity alleviate vasomotor instability by increasing the NE/5-HT balance and therefore NE transmission.

**EXAMPLE 4****Effect of Desipramine on Adrenergic $\alpha_2$  Antagonist-Induced Vasomotor Instability**

[0106] Method as described in the general method section with the following exceptions: Rats were injected subcutaneously with vehicle (sterile H<sub>2</sub>O), atipamezole HCl (selective adrenergic $\alpha_2$  receptor antagonist) (Pfizer, NY, NY, dissolved in sterile H<sub>2</sub>O administered at 0.3 mg/kg), desipramine (dissolved in sterile H<sub>2</sub>O and administered at 1 mg/kg) or with a combination of atipamezole and desipramine. Atipamezole was administered 55 minutes prior to naloxone injection and desipramine was administered 40 minutes prior to naloxone (Figure 6).

[0107] Changes in TST ( $\Delta^{\circ}\text{C}$ , Mean) after naloxone administration demonstrated that atipamezole alone was not significantly different from vehicle treated rats (Figure 6). Desipramine alone abated the naloxone-induced flush by approximately 50% whereas, in combination with atipamezole, an additive effect was noted. The additive effect noted with the combination of atipamezole and desipramine, infer that the adrenergic $\alpha_2$  receptor is involved in vasomotor instability. Furthermore, these data indicated that the efficacy of desipramine was enhanced when administered in combination with an adrenergic $\alpha_2$  receptor antagonist.

**EXAMPLE 5****Functional uptake activity for the Human Monoamine Uptake Transporters****[0108] Cell Lines and Culture Reagents**

MDCK-Net6 cells, stably transfected with human hNET, as described in Pacholczyk, T., R.D. Blakely, and S.G. Amara, *Nature*, 1991, 350(6316): 350-4, were cultured in growth medium containing high glucose DMEM (Gibco, Cat. No. 11995), 10% FBS (dialyzed, heat-inactivated, US Bio-Technologies, Lot FBD1129HI) and 500  $\mu\text{g/ml}$  G418 (Gibco, Cat. No. 10131). Cells were plated at 300,000/ T75 flask and cells were split twice weekly. The JAR cell line (human placental choriocarcinoma) was purchased from ATCC (Cat. No. HTB-144). The cells were cultured in growth medium containing RPMI 1640 (Gibco, Cat. No. 72400), 10% FBS (Irvine, Cat. No. 3000), 1% sodium pyruvate (Gibco, Cat. No.

1136) and 0.25% glucose. Cells were plated at 250,000 cells/T75 flask and split twice weekly. For all assays, cells were plated in Wallac 96-well sterile plates (PerkinElmer, Cat. No. 3983498).

**[0109] Norepinephrine (NE) Uptake Assay**

On day 1, cells were plated at 3,000 cells/well in growth medium and maintained in a cell incubator (37°C, 5% CO<sub>2</sub>). On day 2, growth medium was replaced with 200 µl of assay buffer (25 mM HEPES; 120 mM NaCl; 5 mM KCl; 2.5 mM CaCl<sub>2</sub>; 1.2 mM MgSO<sub>4</sub>; 2 mg/ml glucose (pH 7.4, 37°C)) containing 0.2 mg/ml ascorbic acid and 10 µM pargyline. Plates containing cells with 200 µl of assay buffer were equilibrated for 10 minutes at 37°C prior to addition of compounds. A stock solution of desipramine was prepared in DMSO (10 mM) and delivered to triplicate wells containing cells for a final test concentration of 1 µM. Data from these wells were used to define non-specific NE uptake (minimum NE uptake). Test compounds were prepared in DMSO (10 mM) and diluted in assay buffer according to test range (1 to 10,000 nM). Twenty-five microliters of assay buffer (maximum NE uptake) or test compound were added directly to triplicate wells containing cells in 200 µl of assay buffer. The cells in assay buffer with test compounds were incubated for 20 minutes at 37°C. To initiate the NE uptake, [3H]NE diluted in assay buffer (120 nM final assay concentration) was delivered in 25 µl aliquots to each well and the plates were incubated for 5 minutes (37°C). The reaction was terminated by decanting the supernatant from the plate. The plates containing cells were washed twice with 200 µl assay buffer (37°C) to remove free radioligand. The plates were then inverted, left to dry for 2 minutes, then reinverted and air dried for an additional 10 minutes. The cells were lysed in 25 µl of 0.25 N NaOH solution (4°C), placed on a shake table and vigorously shaken for 5 minutes. After cell lysis, 75 µl of scintillation cocktail was added to each well and the plates were sealed with film tape. The plates were returned to the shake table and vigorously shaken for a minimum of 10 minutes to ensure adequate partitioning of organic and aqueous solutions. The plates were counted in a Wallac Microbeta counter (PerkinElmer) to collect the raw cpm data.

**[0110] Serotonin (5-HT) Uptake Assay**

The methods for 5-HT functional reuptake using the JAR cell line were modified using a previous literature report. Prasad, P.D., *et al.*, *Placenta*, **1996**, 17(4): 201-7. On day 1, cells were plated at 15,000 cells/well in 96-well plates containing growth medium (RPMI 1640 with 10% FBS) and maintained in a cell incubator (37°C, 5% CO<sub>2</sub>). On day 2, cells were stimulated with staurosporine (40 nM) to increase the expression of the 5-HT transporter. On day 3, cells were removed from the cell incubator two hours prior to assay and maintained at room temperature to equilibrate the growth medium to ambient oxygen concentration. Subsequently, the growth medium was replaced with 200 µl of assay buffer (25 mM HEPES; 120 mM NaCl; 5 mM KCl; 2.5 mM CaCl<sub>2</sub>; 1.2 mM MgSO<sub>4</sub>; 2 mg/ml glucose (pH 7.4, 37°C)) containing 0.2 mg/ml ascorbic acid and 10 µM pargyline. A stock solution of paroxetine (AHR-4389-1) was prepared in DMSO (10 mM) and delivered to triplicate wells containing cells for a final test concentration of 1 µM. Data from these wells were used to define non-specific 5-HT uptake (minimum 5-HT uptake). Test compounds were prepared in DMSO (10 mM) and diluted in assay buffer according to test range (1 to 1,000 nM). Twenty-five microliters of assay buffer (maximum 5-HT uptake) or test compound were added directly to triplicate wells containing cells in 200 µl of assay buffer. The cells were incubated with the compound for 10 minutes (37°C). To initiate the reaction, [3H]hydroxytryptamine creatinine sulfate diluted in assay buffer was delivered in 25 µl aliquots to each well for a final test concentration of 15 nM. The cells were incubated with the reaction mixture for 5 minutes at 37°C. The 5-HT uptake reaction was terminated by decanting the assay buffer. The cells were washed twice with 200 µl assay buffer (37°C) to remove free radioligand. The plates were inverted and left to dry for 2 minutes, then reinverted and air-dried for an additional 10 minutes. Subsequently, the cells were lysed in 25 µl of 0.25 N NaOH (4°C) then placed on a shaker table and shaken vigorously for 5 minutes. After cell lysis, 75 µl of scintillation cocktail was added to the wells, the plates were sealed with film tape and replaced on the shake table for a minimum of 10 minutes. The plates were counted in a Wallac Microbeta counter (PerkinElmer) to collect the raw cpm data.

#### [0111] Evaluation of Results

For each experiment, a data stream of cpm values collected from the Wallac

Microbeta counter was downloaded to a Microsoft Excel statistical application program. Determination of percent specific NE uptake (%SB) at 1  $\mu$ M are calculated using a Microsoft Excel spread sheet applying the following formula: [%SB of NE reuptake (%SB) =  $[(1 - (\text{mean cpm control wells} - \text{each cpm drug well}) / (\text{mean cpm control wells} - \text{mean cpm non-specific wells})) \times 100]$ . Calculations of EC<sub>50</sub> values were made using the transformed-both-sides logistic dose response program written by Wyeth Biometrics Department. The statistical program uses mean cpm values from wells representing maximum binding or uptake (assay buffer) and mean cpm values from wells representing minimum binding or uptake ((1  $\mu$ M desipramine (hNET) or 1  $\mu$ M paroxetine (hSERT)). Estimation of the EC<sub>50</sub> value was completed on a log scale and the line was fit between the maximum and minimum binding or uptake values. All graphic data representation was generated by normalizing each data point to a mean percent based on the maximum and minimum binding or uptake values. The EC<sub>50</sub> values reported from multiple experiments were calculated by pooling the raw data from each experiment and analyzing the pooled data as one experiment. The results are shown in Table 1.

Table 1

## Functional uptake activity for the Human Monoamine Uptake Transporters

Compound	hNET EC <sub>50</sub> (nM)	hSERT EC <sub>50</sub> (nM)
desipramine	3.0	392
nisoxetine	7.0	275
1-[1-(3-fluorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol (prepared in accordance with Example 25 of US-A-4,826,844)	240	Inactive at 1 μM
1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol (prepared in accordance with Example 26 of US-A-4,826,844)	55	15,500
1-[2-(4-methyl-1-piperazinyl)-1-[3-(trifluoromethyl)-phenyl]ethyl]cyclohexanol (prepared in accordance with Example 27 of US-A-4,826,844)	87	33,580
	% Specific NE uptake	% Specific NE uptake
1-[1-(4-methoxyphenyl)-2-[4-methyl-1-piperazinyl]ethyl]cyclohexanol (prepared in accordance with Example 28 of US-A-4,826,844)	65	79
1-[1-(3-chlorophenyl)-2-[4-(3-chlorophenyl)-1-piperazinyl]ethyl]cyclohexanol (prepared in accordance with Example 19 of US-A-4,826,844)	23	72
1-[1-(3-methoxyphenyl)-2-[4-(phenylmethyl)-1-piperazinyl]ethyl]cyclohexanol (prepared in accordance with Example 15 of US-A-4,826,844)	43	49
1-[2-(3-chlorophenyl)-1-piperazinyl]-1-[3-methoxyphenyl]ethyl]cyclohexanol (prepared in accordance with Example 18 of US-A-4,826,844)	64	67
1-[2-[4-(6-chloro-2-pyrazinyl)-1-piperazinyl]-1-[3-methoxyphenyl]ethyl]cyclohexanol (prepared in accordance with Example 23 of US-A-4,826,844)	59	58
1-[2-[4-(phenylmethyl)-1-piperazinyl]-1-[3-(trifluoromethyl)phenyl]ethyl]cyclohexanol (prepared in accordance with Example 16 of US-A-4,826,844)	19	94
1-[1-(3-methoxyphenyl)-2-[4-[3-(trifluoromethyl)-phenyl]-1-piperazinyl]ethyl]cyclohexanol (prepared in accordance with Example 20 of US-A-4,826,844)	38	87
1-[1-(4-fluorophenyl)-2-[4-(phenylmethyl)-1-piperazinyl]ethyl]cyclohexanol (prepared in accordance with Example 17 of US-A-4,826,844)	53	88
1-[1-(3-methoxyphenyl)-2-[4-[3-(trifluoromethyl)-phenyl]-1-piperazinyl]ethyl]cyclopentanol (prepared in accordance with Example 21 of US-A-4,826,844)	57	82

**[0112]** When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges specific embodiments therein are intended to be included.

**[0113]** The disclosures of each patent, patent application and publication cited or described in this document are hereby incorporated herein by reference, in its entirety.

**[0114]** Those skilled in the art will appreciate that numerous changes and modifications can be made to the preferred embodiments of the invention and that such changes and modifications can be made without departing from the spirit of the invention. It is, therefore, intended that the appended claims cover all such equivalent variations as fall within the true spirit and scope of the invention.

What is claimed is:

1. A method for treating or preventing vasomotor symptoms in a subject in need thereof, comprising the step of:  
     administering to said subject a composition, comprising:  
     a therapeutically effective amount of at least one norepinephrine reuptake inhibitor or pharmaceutically acceptable salt thereof.
2. A method according to claim 1,  
     wherein said compound has a selectivity ratio of SERT:NET of less than about 1,000:1.
3. A method according to claim 1,  
     wherein said compound has a selectivity ratio of SERT:NET of greater than about 2:1.
4. A method according to claim 1,  
     wherein said compound has a selectivity ratio of SERT:NET of greater than about 5:1.
5. A method according to claim 1,  
     wherein said compound has a selectivity ratio of SERT:NET of greater than about 10:1.
6. A method according to claim 1,  
     wherein said norepinephrine reuptake inhibitor is selected from the group consisting of: maprotiline; reboxetine; norpramine; desipramine; nisoxetine; atomoxetine; amoxapine; doxepin; lofepramin; amitriptyline; 1-[1-(3-fluorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol; 1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol; 1-[2-(4-methyl-1-piperazinyl)-1-[3-(trifluoromethyl)-phenyl]ethyl]cyclohexanol; 1-[1-(4-methoxyphenyl)-2-[4-methyl-1-piperazinyl]ethyl]cyclohexanol; 1-[1-(3-chlorophenyl)-2-[4-(3-chlorophenyl)-1-piperazinyl]ethyl]cyclohexanol; 1-[1-(3-methoxyphenyl)-

2-[4-phenyl methyl)-1-piperazinyl]ethyl]cyclohexanol; 1-[2-(3-chloro phenyl)1-piperazinyl]-1-[3-methoxyphenyl]ethyl]cyclohexanol; 1-[2-[4-(6-chloro-2-pyrazinyl)-1-piperazinyl]-1-[3-methoxyphenyl]ethyl]cyclohexanol; 1-[2-[4-(phenyl methyl)]-1-piperazinyl]-1-[3-(trifluoromethyl)phenyl]ethyl]cyclohexanol; 1-[1-(3-methoxyphenyl)-2-[4-[3-(trifluoromethyl)-phenyl]-1-piperazinyl]ethyl]cyclohexanol; 1-[1-(4-fluorophenyl)-2-[4-(phenylmethyl)-1-piperazinyl] ethyl]cyclohexanol; 1-[1-(3-methoxyphenyl)-2-[4-[3-(trifluoromethyl)-phenyl]-1-piperazinyl]ethyl]cyclopentanol; 1-[1-(4-fluorophenyl)-2-[4-(phenylmethyl)-1-piperazinyl]ethyl]cyclohexanol; 1-[2-(dimethylamino)-1-(3-trifluoromethyl phenyl)ethyl]cyclohexanol; 1-[1-(3-fluorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol; 1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol; 1-[2-dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol; 1-[1-(3-chlorophenyl)-2-piperazin-1-yl-ethyl]-cyclohexanol; and combinations and pharmaceutically acceptable salts thereof.

7. A method according to claim 6,  
wherein said norepinephrine reuptake inhibitor is desipramine or pharmaceutically acceptable salt thereof.
8. A method according to claim 6,  
wherein said norepinephrine reuptake inhibitor is 1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol or pharmaceutically acceptable salt thereof.
9. A method according to claim 8,  
wherein said norepinephrine reuptake inhibitor is a pure enantiomer of 1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol.
10. A method according to claim 1,  
wherein said composition further comprises a therapeutically effective amount of at least one serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof.

11. A method according to claim 10,  
wherein said serotonin reuptake inhibitor is selected from the group consisting of fluoxetine, paroxetine, sertraline, fluvoxamine, and combinations and pharmaceutically acceptable salts thereof.
12. A method according to claim 10,  
wherein said norepinephrine reuptake inhibitor and said serotonin reuptake inhibitor are administered concurrently.
13. A method according to claim 1,  
wherein said composition further comprises a therapeutically effective amount of at least one adrenergic $\alpha_2$  receptor antagonist or a pharmaceutically acceptable salt thereof.
14. A method according to claim 13,  
wherein said norepinephrine reuptake inhibitor and said adrenergic $\alpha_2$  receptor antagonist are administered concurrently.
15. A method according to claim 13,  
wherein said norepinephrine reuptake inhibitor and said adrenergic $\alpha_2$  receptor antagonist are administered simultaneously.
16. A method according to claim 13,  
wherein said norepinephrine reuptake inhibitor and said adrenergic $\alpha_2$  receptor antagonist are a single compound.
17. A method according to claim 13,  
wherein said adrenergic $\alpha_2$  receptor antagonist is a compound selected from the group consisting of atipamezole; 2-[2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl]-4,4-dimethyl-1,3-(2H,4H)-isoquinolinindione dihydrochloride (ARC 239 dihydrochloride); 2-[(4,5-dihydro-1H-imidazol-2-yl)methyl]-2,3-dihydro-1-methyl-1H-isoindole maleate (BRL

WO 2004/035058

PCT/US2003/032759

44408 maleate); BRL48962; BRL41992; SKF 104856; SKF 104078; MK912; 2-(2-ethyl-2,3-dihydro-2-benzofuranyl)-4,5-dihydro-1H-imidazole hydrochloride (efaroxan hydrochloride); 2-(1,4-benzodioxan-2-yl)-2-imidazoline hydrochloride (idazoxan hydrochloride); 2-(1-ethyl-2-indazolyl)methyl-1,4-benzodioxan hydrochloride (imiloxan hydrochloride); 17 $\alpha$ -hydroxy-20 $\alpha$ -yohimban-16 $\beta$ -carboxylic acid, methyl ester hydrochloride (rauwolscine hydrochloride); (8 $\alpha$ R,12 $\alpha$ S,13 $\alpha$ S)-5,8,8 $\alpha$ ,9,10,11,12,12 $\alpha$ ,13,13 $\alpha$ -dehydro-3-methoxy-12-(ethylsulfonyl)-6H-isoquino[2,1- $\gamma$ ][1,6]naphthyridine hydrochloride (RS 79948 hydrochloride); 2-(2,3-dihydro-2-methoxy-1,4-benzodioxin-2-yl)-4,5-dihydro-1H-imidazole hydrochloride (RX 821002 hydrochloride); 8-[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one (spiroxatrine); 17 $\alpha$ -hydroxy-yohimban-16 $\alpha$ -carboxylic acid methyl ester hydrochloride (yohimbine hydrochloride); and combinations and pharmaceutically acceptable salts thereof.

18. A method according to claim 13,  
wherein said adrenergic $\alpha_2$  receptor antagonist is selective for the adrenergic $\alpha_{2A}$  receptor.
19. A method according to claim 13,  
wherein said adrenergic $\alpha_2$  receptor antagonist is selective for the adrenergic $\alpha_{2B}$  receptor.
20. A method according to claim 13,  
wherein said adrenergic $\alpha_2$  receptor antagonist is selective for the adrenergic $\alpha_{2C}$  receptor.
21. A method according to claim 13,  
wherein said adrenergic $\alpha_2$  receptor antagonist is selective for the adrenergic $\alpha_{2D}$  receptor.

22. A method according to claim 1,  
wherein said pharmaceutically acceptable salt is an acid addition salt.
23. A method according to claim 1,  
wherein said vasomotor symptom is hot flush.
24. A method according to claim 1,  
wherein said subject is human.
25. A method according to claim 24,  
wherein said human is a female.
26. A method according to claim 25,  
wherein said female is pre-menopausal.
27. A method according to claim 25,  
wherein said female is peri-menopausal.
28. A method according to claim 25,  
wherein said female is post-menopausal.
29. A method according to claim 24,  
wherein said human is a male.
30. A method according to claim 29,  
wherein said male is naturally, chemically or surgically andropausal.
31. A pharmaceutical composition, comprising:
  - a. at least one norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof;
  - b. at least one serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof; and
  - c. at least one pharmaceutically acceptable carrier.

32. A pharmaceutical composition according to claim 31,  
wherein said pharmaceutically acceptable salt is an acid addition salt.
33. A pharmaceutical composition according to claim 31,  
wherein said norepinephrine reuptake inhibitor is selected from the group consisting of: maprotiline; reboxetine; norpramine, desipramine; nisoxetine; atomoxetine; amoxapine; doxepin; lofepramin; amitriptyline; 1-[1-(3-fluorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol; 1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl) ethyl]cyclohexanol; 1-[2-(4-methyl-1-piperazinyl)-1-[3-(trifluoromethyl)-phenyl]ethyl] cyclohexanol; 1-[1-(4-methoxyphenyl)-2-[4-methyl-1-piperazinyl)ethyl]cyclohexanol; 1-[1-(3-chlorophenyl)-2-[4-(3-chlorophenyl)-1-piperazinyl]ethyl]cyclohexanol; 1-[1-(3-methoxyphenyl)-2-[4-phenyl methyl)-1-piperazinyl]ethyl]cyclohexanol; 1-[2-(3-chloro phenyl)1-piperazinyl]-1-[3-methoxyphenyl)ethyl]cyclohexanol; 1-[2-[4-(6-chloro-2-pyrazinyl)-1-piperazinyl]-1-[3-methoxyphenyl)ethyl]cyclohexanol; 1-[2-[4-(phenyl methyl)-1-piperazinyl]-1-[3-(trifluoromethyl)phenyl]ethyl]cyclohexanol; 1-[1-(3-methoxyphenyl)-2-[4-[3-(trifluoro methyl)-phenyl]-1-piperazinyl]ethyl] cyclohexanol; 1-[1-(4-fluorophenyl)-2-[4-(phenylmethyl)-1-piperazinyl] ethyl] cyclohexanol; 1-[1-(3-methoxyphenyl)-2-[4-[3-(trifluoromethyl)-phenyl]-1-piperazinyl]ethyl]cyclopentanol; 1-[1-(4-fluorophenyl)-2-[4-(phenylmethyl)-1-piperazinyl]ethyl]cyclohexanol; 1-[2-(dimethylamino)-1-(3-trifluoromethyl phenyl)ethyl]cyclohexanol; 1-[1-(3-fluorophenyl)-2-(4-methyl-1-piperazinyl) ethyl]cyclohexanol; 1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl] cyclohexanol; 1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol; 1-[2-dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol; 1-[1-(3-chlorophenyl)-2-piperazin-1-yl-ethyl]-cyclohexanol; and combinations and pharmaceutically acceptable salts thereof.
34. A pharmaceutical composition according to claim 31,  
wherein said norepinephrine reuptake inhibitor is desipramine.
35. A pharmaceutical composition according to claim 31,

- wherein said norepinephrine reuptake inhibitor is 1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol.
36. A pharmaceutical composition according to claim 35,  
wherein said norepinephrine reuptake inhibitor is a pure enantiomer of 1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol.
37. A pharmaceutical composition according to claim 31,  
wherein said serotonin reuptake inhibitor is selected from the group consisting of fluoxetine, paroxetine, sertraline, fluvoxamine, and combinations and pharmaceutically acceptable salts thereof.
38. A pharmaceutical composition, comprising:
- at least one norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof;
  - one adrenergic $\alpha_2$  receptor antagonist or a pharmaceutically acceptable salt thereof; and
  - at least one pharmaceutically acceptable carrier.
39. A pharmaceutical composition according to claim 38,  
wherein said pharmaceutically acceptable salt is an acid addition salt.
40. A pharmaceutical composition according to claim 38,  
wherein said norepinephrine reuptake inhibitor is selected from the group consisting of: maprotiline; reboxetine; norpramine, desipramine; nisoxetine; atomoxetine; amoxapine; doxepin; lofepramin; amitriptyline; 1-[1-(3-fluorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol; 1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol; 1-[2-(4-methyl-1-piperazinyl)-1-[3-(trifluoromethyl)-phenyl]ethyl]cyclohexanol; 1-[1-(4-methoxyphenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol; 1-[1-(3-chlorophenyl)-2-[4-(3-chlorophenyl)-1-piperazinyl]ethyl]cyclohexanol; 1-[1-(3-methoxyphenyl)-2-[4-phenyl methyl)-1-piperazinyl]ethyl]cyclohexanol; 1-[2-(3-chlorophenyl)-1-piperazinyl]-1-[3-methoxyphenyl]ethyl]cyclohexanol; 1-[2-[4-(6-chloro-2-

WO 2004/035058

PCT/US2003/032759

pyrazinyl)-1-piperazinyl]-1-[3-methoxyphenyl]ethyl]cyclohexanol; 1-[2-[4-(phenyl methyl)]-1-piperazinyl]-1-[3-(trifluoromethyl)phenyl]ethyl]cyclohexanol; 1-[1-(3-methoxyphenyl)-2-[4-[3-(trifluoromethyl)-phenyl]-1-piperazinyl]ethyl]cyclohexanol; 1-[1-(4-fluorophenyl)-2-[4-(phenylmethyl)-1-piperazinyl]ethyl]cyclohexanol; 1-[1-(3-methoxyphenyl)-2-[4-[3-(trifluoromethyl)-phenyl]-1-piperazinyl]ethyl]cyclopentanol; 1-[1-(4-fluorophenyl)-2-[4-(phenylmethyl)-1-piperazinyl]ethyl]cyclohexanol; 1-[2-(dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol; 1-[1-(3-fluorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol; 1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol; 1-[2-dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol; 1-[1-(3-chlorophenyl)-2-piperazin-1-yl-ethyl]-cyclohexanol; and combinations and pharmaceutically acceptable salts thereof.

41. A pharmaceutical composition according to claim 40,  
wherein said norepinephrine reuptake inhibitor is desipramine.
42. A pharmaceutical composition according to claim 40,  
wherein said norepinephrine reuptake inhibitor is 1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol.
43. A pharmaceutical composition according to claim 42,  
wherein said norepinephrine reuptake inhibitor is a pure enantiomer of 1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol.
44. A pharmaceutical composition according to claim 38,  
wherein said adrenergic<sub>α2</sub> receptor antagonist is a compound selected from the group consisting of atipamezole; 2-[2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl]-4,4-dimethyl-1,3-(2H,4H)-isoquinolindione dihydrochloride (ARC 239 dihydrochloride); 2-[(4,5-dihydro-1H-imidazol-2-yl)methyl]-2,3-dihydro-1-methyl-1H-isoindole maleate (BRL 44408 maleate); BRL48962; BRL41992; SKF 104856; SKF 104078; MK912; 2-(2-ethyl-2,3-dihydro-2-benzofuranyl)-4,5-dihydro-1H-imidazole hydrochloride (efaroxan hydrochloride); 2-(1,4-benzodioxan-2-yl)-2-

imidazoline hydrochloride (idazoxan hydrochloride); 2-(1-ethyl-2-indazolyl)methyl-1,4-benzodioxan hydrochloride (imiloxan hydrochloride); 17 $\alpha$ -hydroxy-20 $\alpha$ -yohimban-16 $\beta$ -carboxylic acid, methyl ester hydrochloride (rauwolscine hydrochloride); (8 $\alpha$ R,12 $\alpha$ S,13 $\alpha$ S)-5,8,8 $\alpha$ ,9,10,11,12,12 $\alpha$ ,13,13 $\alpha$ -dehydro-3-methoxy-12-(ethylsulfonyl)-6H-isoquino[2,1- $\gamma$ ][1,6]naphthyridine hydrochloride (RS 79948 hydrochloride); 2-(2,3-dihydro-2-methoxy-1,4-benzodioxin-2-yl)-4,5-dihydro-1H-imidazole hydrochloride (RX 821002 hydrochloride); 8-[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one (spiroxatrine); 17 $\alpha$ -hydroxyyohimban-16 $\alpha$ -carboxylic acid methyl ester hydrochloride (yohimbine hydrochloride); and combinations and pharmaceutically acceptable salts thereof.

45. A pharmaceutical composition according to claim 38,  
wherein said adrenergic $\alpha_2$  receptor antagonist is selective for the adrenergic $\alpha_{2A}$  receptor.
46. A pharmaceutical composition according to claim 38,  
wherein said adrenergic $\alpha_2$  receptor antagonist is selective for the adrenergic $\alpha_{2B}$  receptor.
47. A pharmaceutical composition according to claim 38,  
wherein said adrenergic $\alpha_2$  receptor antagonist is selective for the adrenergic $\alpha_{2C}$  receptor.
48. A pharmaceutical composition according to claim 38,  
wherein said adrenergic $\alpha_2$  receptor antagonist is selective for the adrenergic $\alpha_{2D}$  receptor.
49. A use of a norepinephrine reuptake inhibitor for the manufacture of a medicament for preventing or treating vasomotor symptoms in a human.

WO 2004/035058

PCT/US2003/032759

50. A use of a norepinephrine reuptake inhibitor in combination with a serotonin reuptake inhibitor for the manufacture of a medicament for preventing or treating vasomotor symptoms in a human.
51. A use of a norepinephrine reuptake inhibitor in combination with a adrenergic $\alpha_2$  receptor antagonist for the manufacture of a medicament for preventing or treating vasomotor symptoms in a human.

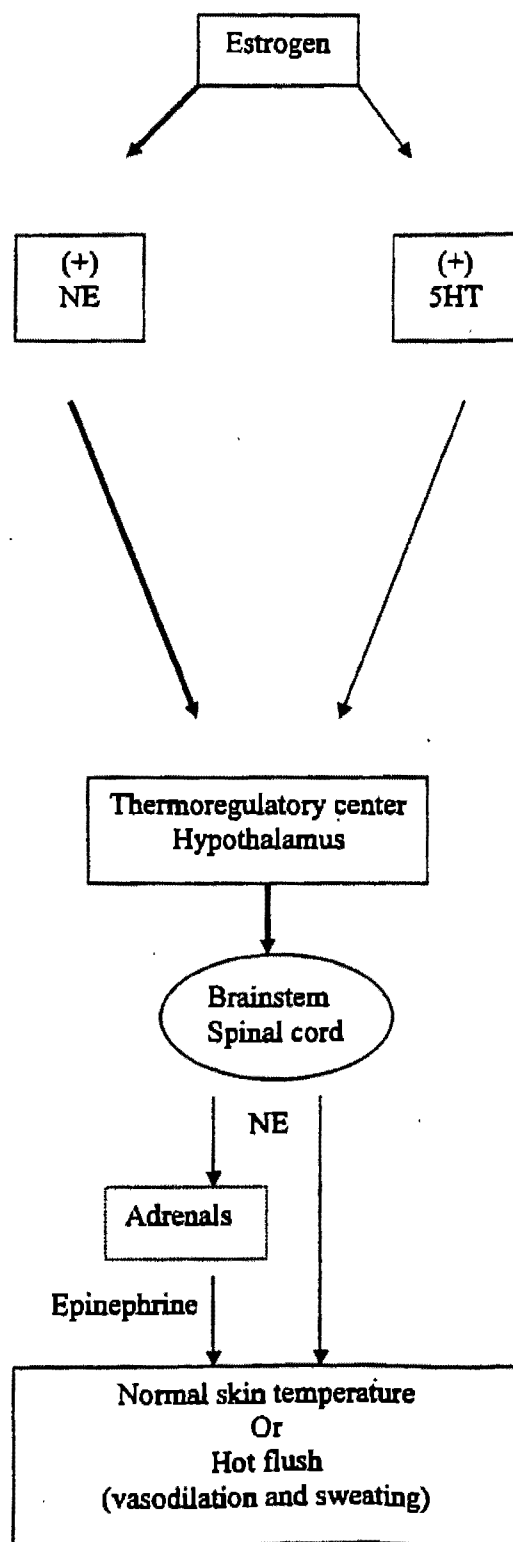
**FIGURE 1**

FIGURE 2

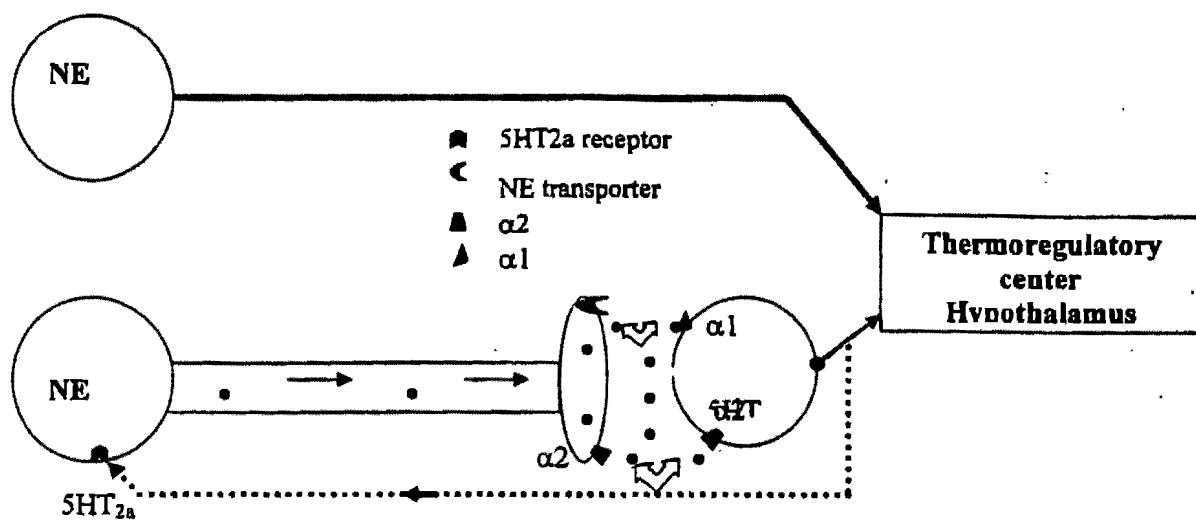
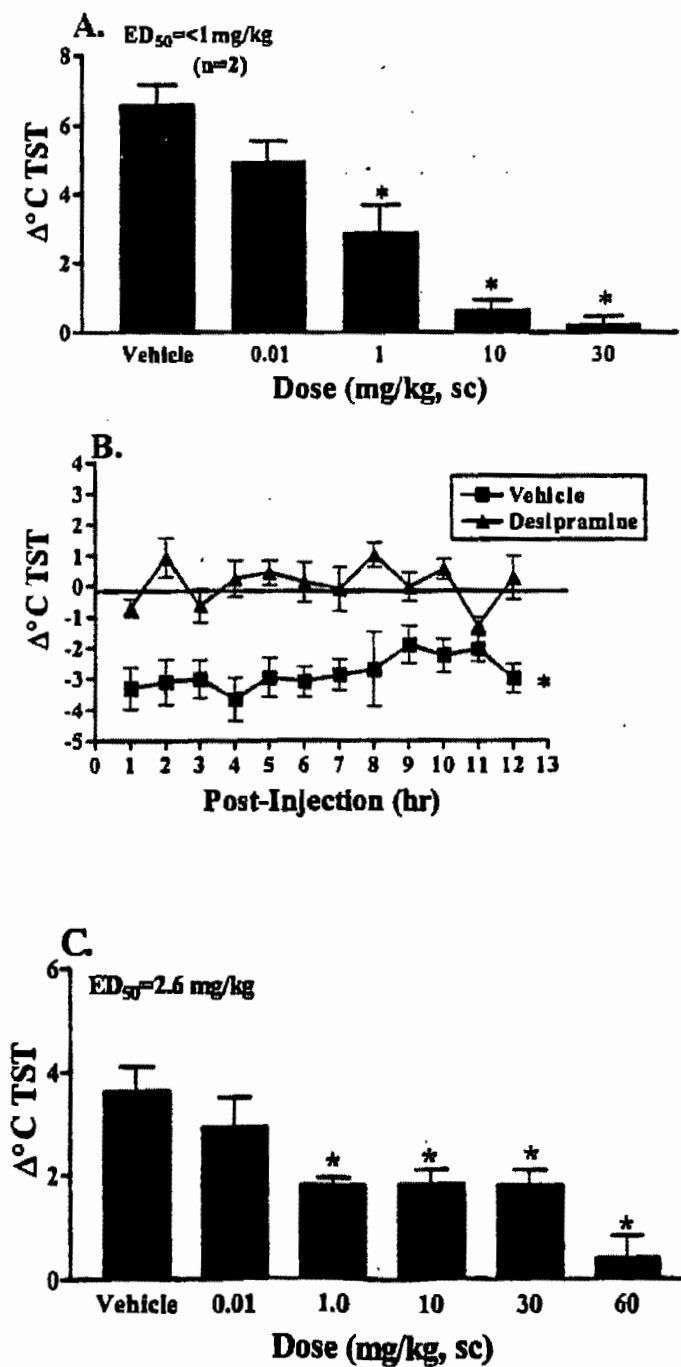
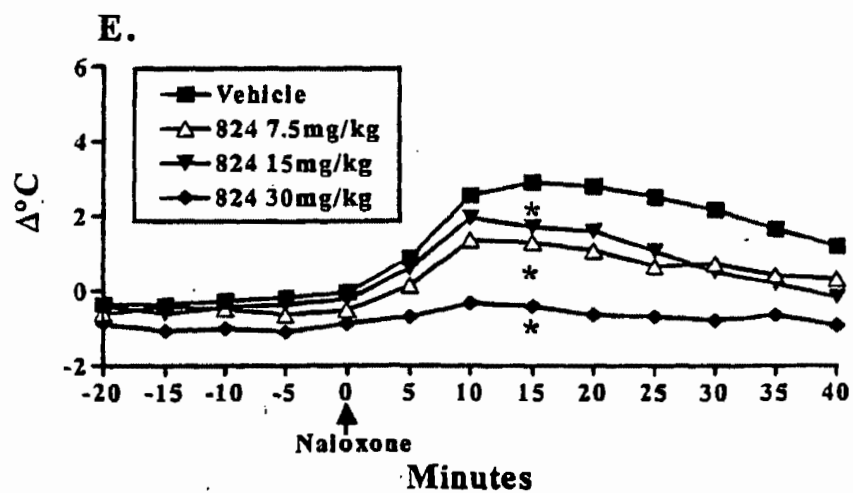
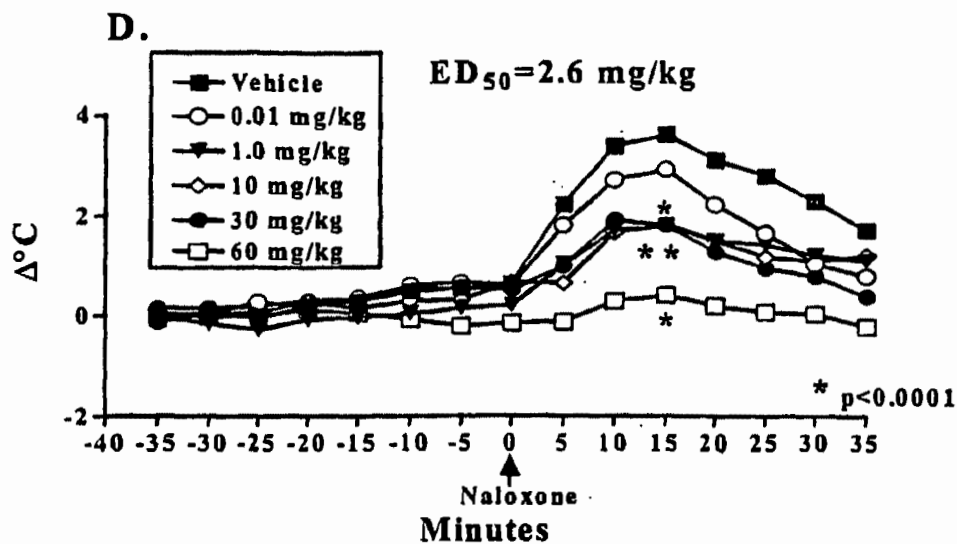
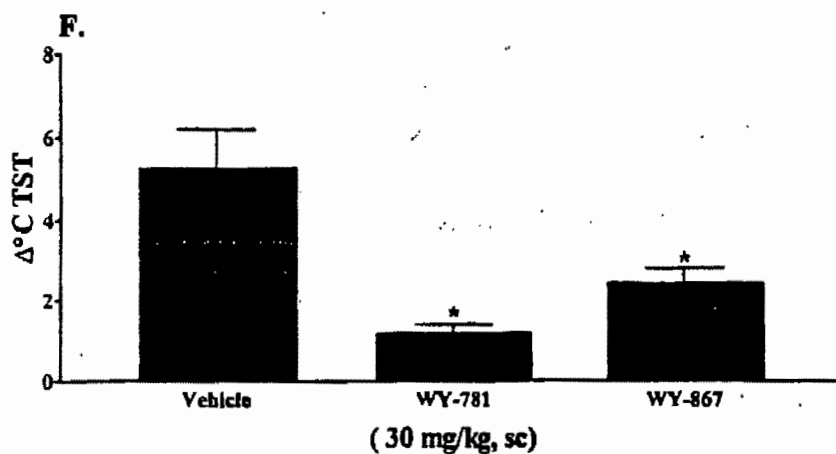
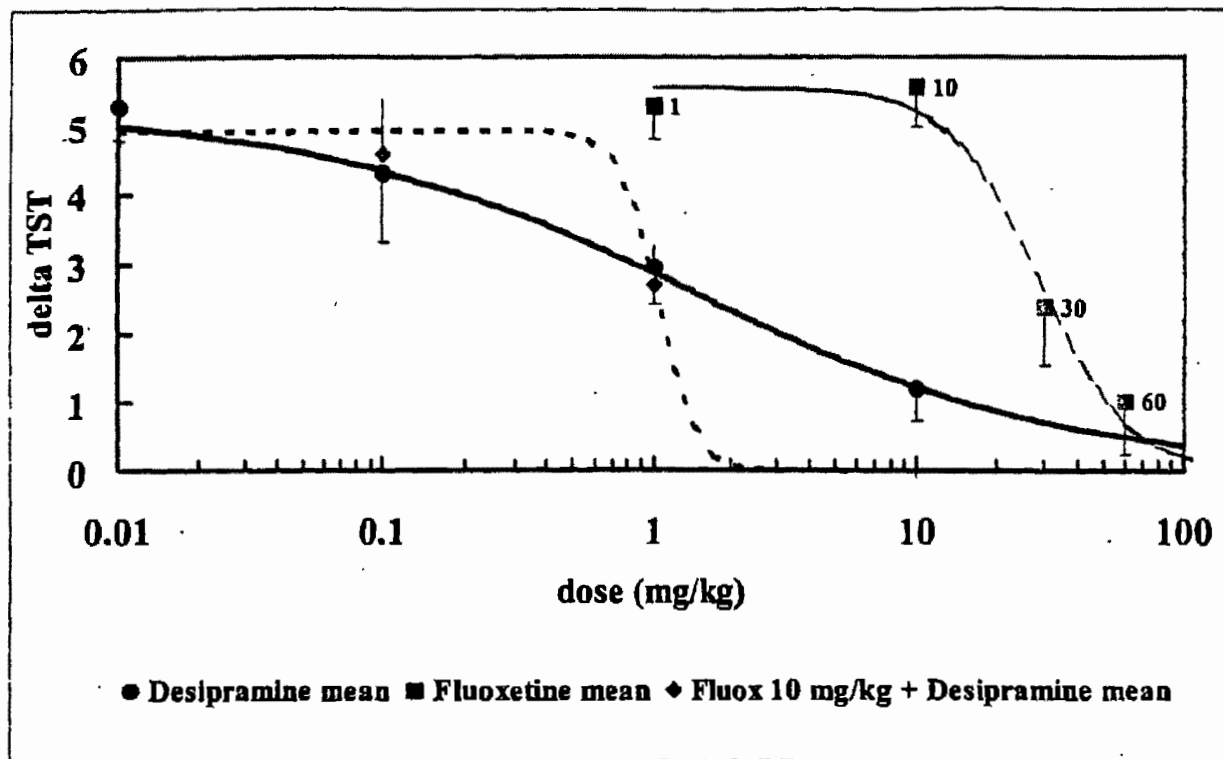


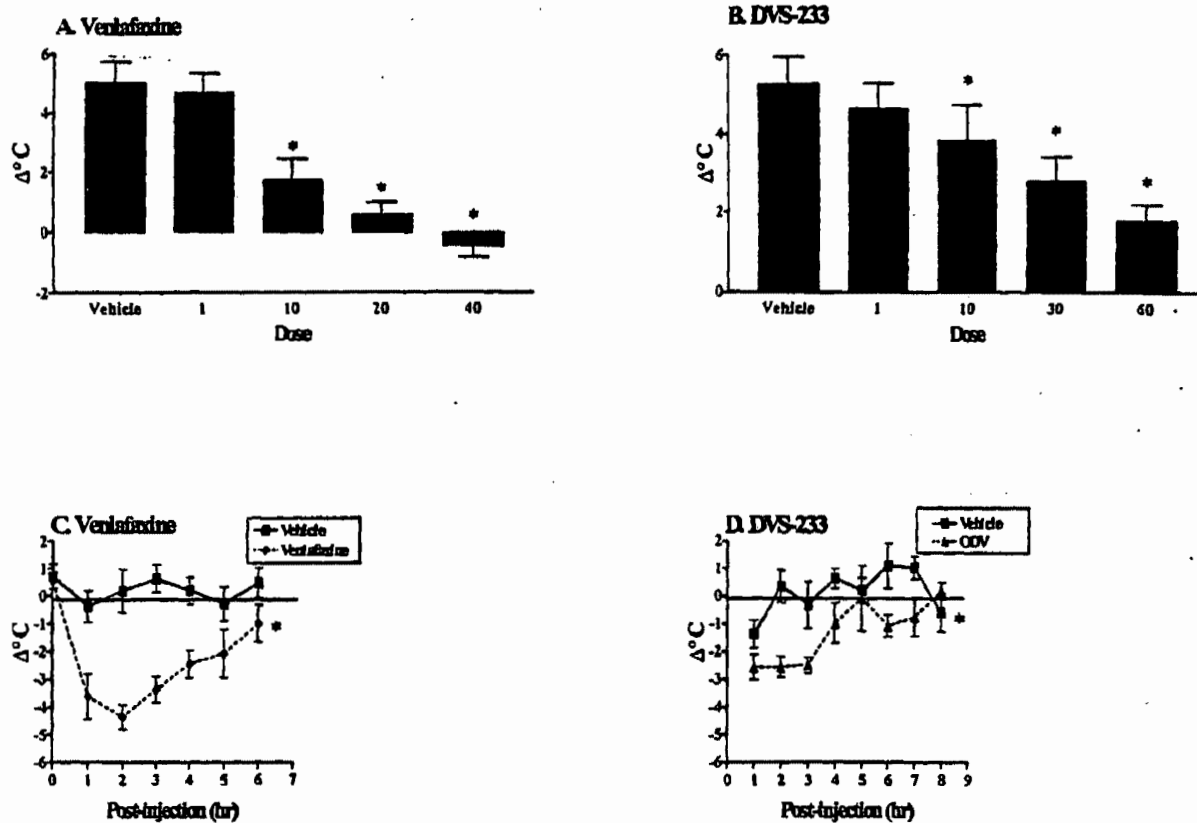
FIGURE 3





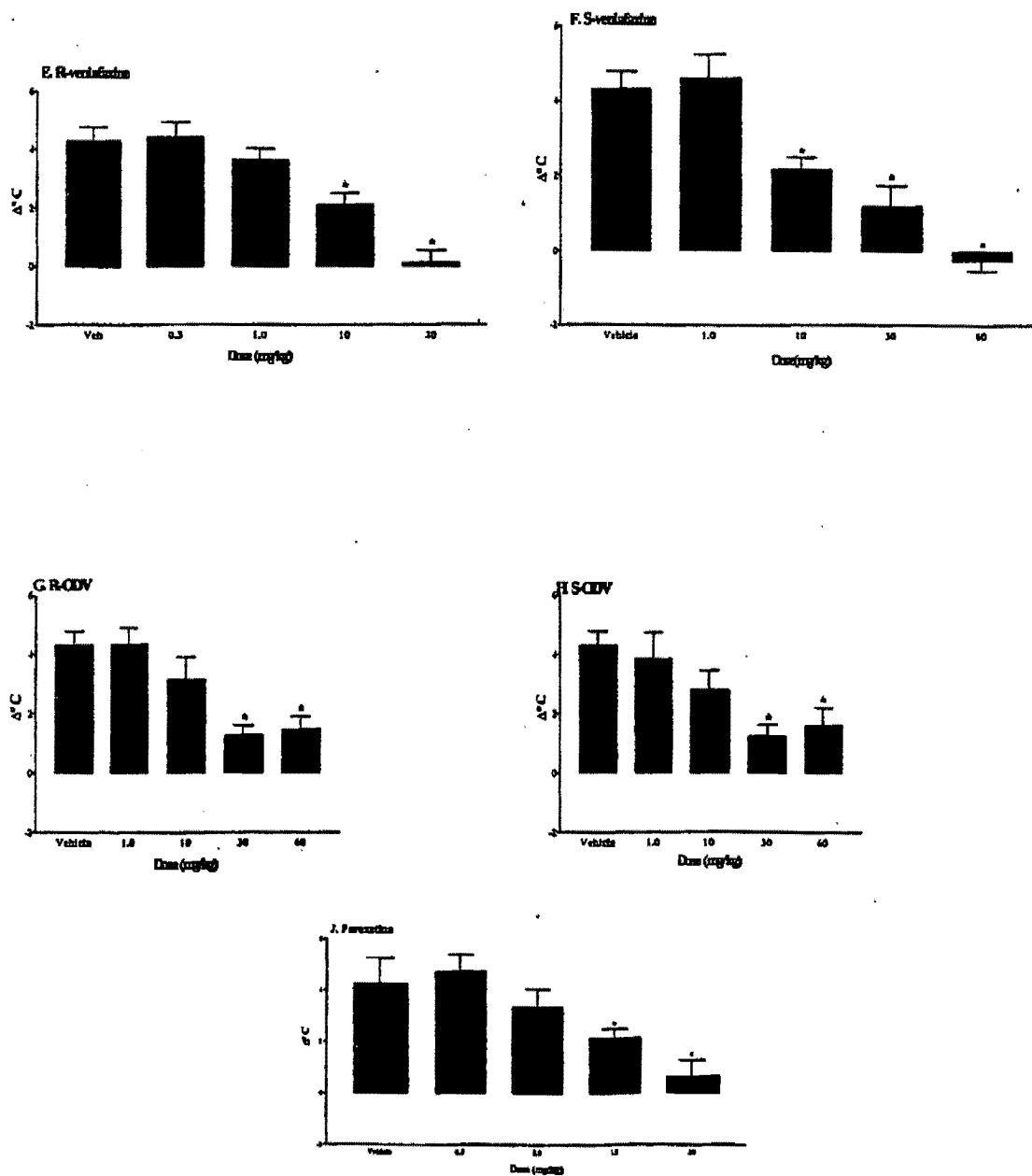


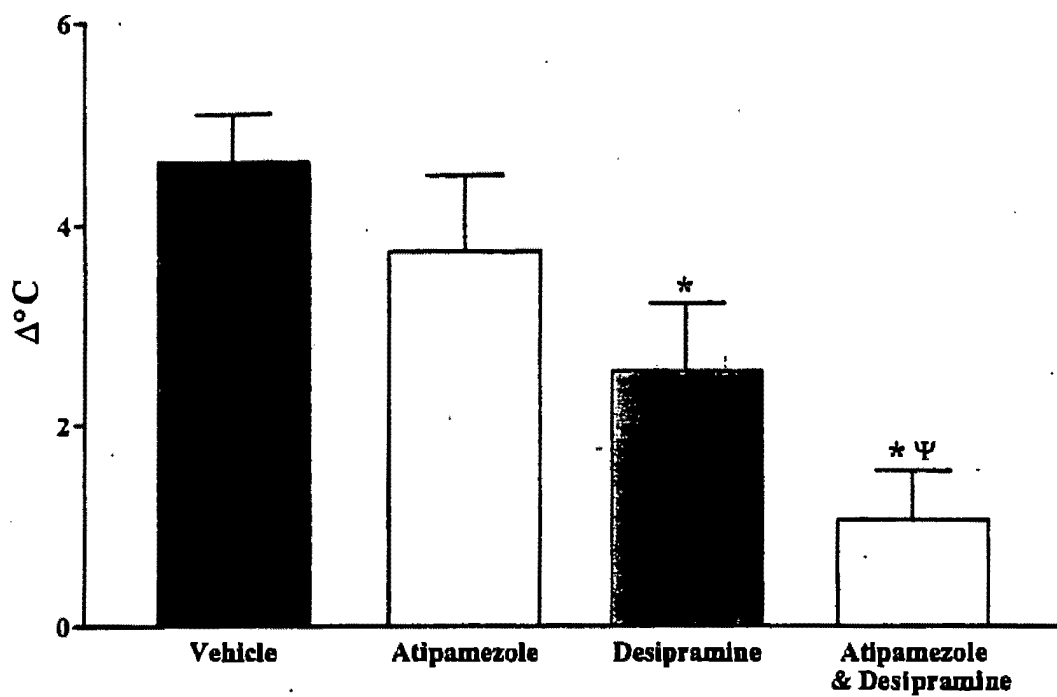
**FIGURE 4**

**FIGURE 5**

WO 2004/035058

PCT/US2003/032759



**FIGURE 6****15 min post-naloxone: Atipamezole (0.3 mg/kg)+ Desipramine (1.0 mg/kg)**

## INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/US 03/32759

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/55 A61K31/5377 A61K31/138 A61K31/4174 A61K31/496  
 A61K31/497 A61K31/137 A61P5/00 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 03 037334 A (ALVES STEPHEN E ;MERCK & CO INC (US); WRIGHT SAMUEL D (US); HAMMON) 8 May 2003 (2003-05-08) page 13, line 3-5, 13, 14, 17, 18; claims 7, 8, 12, 14, 23	1-7, 22-30, 49
X	EP 0 303 961 A (MERRELL DOW PHARMA) 22 February 1989 (1989-02-22) claims 17-21; table 1	31-34, 37
X	US 4 310 524 A (WIECH NORBERT L ET AL) 12 January 1982 (1982-01-12) claims 1, 9, 14	38-41, 44-48
X	EP 0 065 757 A (MERCK & CO INC) 1 December 1982 (1982-12-01) page 2, line 29-32	38, 39
	-/-	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
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- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*S\* document member of the same patent family

Date of the actual completion of the international search

5 March 2004

Date of mailing of the international search report

23/03/2004

Name and mailing address of the ISA

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 Fax: (+31-70) 340-3016

Authorized officer

Ansaldo, M

## INTERNATIONAL SEARCH REPORT

Intern: Application No

PCT/US 03/32759

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>RENERIC JEAN-PHILIPPE ET AL: "Idazoxan and 8-OH-DPAT modify the behavioral effects induced by either NA, or 5-HT, or dual NA/5-HT reuptake inhibition in the rat forced swimming test"</p> <p>NEUROPSYCHOPHARMACOLOGY, vol. 24, no. 4, April 2001 (2001-04), pages 379-390, XP001179758 ISSN: 0893-133X abstract</p>	38-41, 44-48

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 03 82759

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-5, 10,12-16, 18-30, 31-32, 38-39, 45-51 (in part)

Present claims 1-5, 10,12-16, 18-21,22-30, 31-32, 38-39, 45-48, 49-51 relate to an extremely large number of possible compounds (norepinephrine reuptake inhibitors, serotonin reuptake inhibitors, adrenergic alpha 2 receptor antagonists). Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds mentioned in claims 6-9, 11, 17, 33-37, 40-44 and in the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

International application No.  
PCT/US 03/32759

## INTERNATIONAL SEARCH REPORT

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 1-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-5, 10, 12-16, 18-30, 31-32, 38-39, 45-51 (in part)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No

PCT/US 03/32759

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03037334	A	08-05-2003	WO 03037334 A1	08-05-2003
EP 0303961	A	22-02-1989	AT 104269 T	15-04-1994
			AU 606444 B2	07-02-1991
			AU 2057988 A	16-02-1989
			AU 624278 B2	04-06-1992
			AU 6598990 A	24-01-1991
			CA 1327795 C	15-03-1994
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			DE 3889032 D1	19-05-1994
			DE 3889032 T2	11-08-1994
			DK 454688 A	15-02-1989
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			FI 883739 A ,B,	15-02-1989
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			JP 1066151 A	13-03-1989
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			KR 126137 B1	26-12-1997
			NO 883595 A ,B,	15-02-1989
			NZ 225758 A	26-10-1990
			PT 88251 A ,B	30-06-1989
			US 6136803 A	24-10-2000
			US 5561152 A	01-10-1996
			US 5149714 A	22-09-1992
			US 5880120 A	09-03-1999
			ZA 8805824 A	26-04-1989
US 4310524	A	12-01-1982	NONE	
EP 0065757	A	01-12-1982	AT 11134 T	15-01-1985
			AU 547319 B2	17-10-1985
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			CA 1214467 A1	25-11-1986
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			ES 8306740 A1	16-09-1983
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			IL 65802 A	31-12-1985
			JP 1332750 C	28-08-1986
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			NO 821730 A	29-11-1982
			NZ 200642 A	09-11-1984
			PH 18686 A	29-08-1985
			PT 74926 A ,B	01-06-1982
			US 4456604 A	26-06-1984
			ZA 8203611 A	28-12-1983

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

<b>PATENT APPLICATION FEE DETERMINATION RECORD</b> Substitute for Form PTO-875					Application or Docket Number <b>14/577,227</b>		Filing Date <b>12/19/2014</b>		<input type="checkbox"/> To be Mailed			
ENTITY: <input checked="" type="checkbox"/> LARGE <input type="checkbox"/> SMALL <input type="checkbox"/> MICRO												
<b>APPLICATION AS FILED – PART I</b>												
(Column 1)			(Column 2)									
FOR		NUMBER FILED		NUMBER EXTRA		RATE (\$)		FEE (\$)				
<input type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A		N/A		N/A						
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (l), or (m))		N/A		N/A		N/A						
<input type="checkbox"/> EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A		N/A		N/A						
TOTAL CLAIMS (37 CFR 1.16(i))		minus 20 =		*		X \$ =						
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 =		*		X \$ =						
<input type="checkbox"/> APPLICATION SIZE FEE (37 CFR 1.16(s))		If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).										
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))												
* If the difference in column 1 is less than zero, enter "0" in column 2.						TOTAL						
<b>APPLICATION AS AMENDED – PART II</b>												
(Column 1)			(Column 2)			(Column 3)						
AMENDMENT	<b>08/07/2015</b>		CLAIMS REMAINING AFTER AMENDMENT			HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))		* 14		Minus	** 20	= 0		X \$80 =		0	
	Independent (37 CFR 1.16(h))		* 1		Minus	*** 3	= 0		X \$420 =		0	
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))											
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))											
	TOTAL ADD'L FEE										<b>0</b>	
(Column 1)			(Column 2)			(Column 3)						
AMENDMENT			CLAIMS REMAINING AFTER AMENDMENT			HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))		*		Minus	**	=		X \$ =			
	Independent (37 CFR 1.16(h))		*		Minus	***	=		X \$ =			
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))											
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))											
	TOTAL ADD'L FEE											
<p>* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.</p> <p>** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".</p> <p>*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".</p> <p>The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.</p>												

LDRC  
/EVA GILLIS/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

'237 FH -0148



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 United States Patent and Trademark Office  
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 P.O. Box 1450  
 Alexandria, Virginia 22313-1450  
 www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
14/577,227	12/19/2014	1629	0.00	091856-0158	14	1

CONFIRMATION NO. 5836

UPDATED FILING RECEIPT

22428

Foley & Lardner LLP  
 3000 K STREET N.W.  
 SUITE 600  
 WASHINGTON, DC 20007-5109



CC000000076895044

Date Mailed: 08/18/2015

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

**Inventor(s)**

Patricia Allison Tewes Richards, Scarsdale, NY;

**Applicant(s)**

Patricia Allison Tewes Richards, Scarsdale, NY;

**Assignment For Published Patent Application**

Noven Therapeutics, LLC, Miami, FL

**Power of Attorney:** None**Domestic Priority data as claimed by applicant**

This application is a CON of 14/157,992 01/17/2014 PAT 8946251  
 which is a CON of 12/292,960 12/01/2008 PAT 8658663  
 which is a CON of 11/499,586 08/04/2006 ABN

**Foreign Applications** for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

*Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.*

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

**If Required, Foreign Filing License Granted:** 01/08/2015

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/577,227**

**Projected Publication Date:** 11/26/2015

**Non-Publication Request:** No

**Early Publication Request:** No  
**Title**

METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE

**Preliminary Class**

514

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

## **PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES**

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

**LICENSE FOR FOREIGN FILING UNDER**  
**Title 35, United States Code, Section 184**  
**Title 37, Code of Federal Regulations, 5.11 & 5.15**

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The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

**NOT GRANTED**

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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<b>PATENT APPLICATION FEE DETERMINATION RECORD</b>						Application or Docket Number 14/577,227			
Substitute for Form PTO-875									
<b>APPLICATION AS FILED - PART I</b>									
(Column 1)		(Column 2)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY			
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)		
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280		
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600		
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720		
TOTAL CLAIMS (37 CFR 1.16(i))	14	minus 20 = *			OR	x 80 =	0.00		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1	minus 3 = *				x 420 =	0.00		
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00		
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00		
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1600		
<b>APPLICATION AS AMENDED - PART II</b>									
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY	
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)	
	Total (37 CFR 1.16(i))	*	Minus	**	=	OR	x	=	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	OR	x	=	
	Application Size Fee (37 CFR 1.16(s))					OR			
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					OR			
			TOTAL ADD'L FEE			OR	TOTAL ADD'L FEE		
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)	
	Total (37 CFR 1.16(i))	*	Minus	**	=	OR	x	=	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	OR	x	=	
	Application Size Fee (37 CFR 1.16(s))					OR			
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					OR			
			TOTAL ADD'L FEE			OR	TOTAL ADD'L FEE		
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.									



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/577,227	12/19/2014	Patricia Allison Tewes Richards	091856-0158

22428  
 Foley & Lardner LLP  
 3000 K STREET N.W.  
 SUITE 600  
 WASHINGTON, DC 20007-5109

**CONFIRMATION NO. 5836**  
**IMPROPER CPOA LETTER**



Date Mailed: 08/18/2015

## NOTICE REGARDING POWER OF ATTORNEY

This is in response to the power of attorney filed 08/07/2015. The power of attorney in this application is not accepted for the reason(s) listed below:

- The power of attorney has not been accepted because the party who is giving power has not been identified. Power of attorney may only be signed by the applicant for patent (37 CFR 1.42) or the patent owner. A party who is not the applicant must become the applicant in accordance with 37 CFR 1.46(c) and appoint any power of attorney in compliance with 37 CFR 3.71 and 3.73. For a reissue application, reexamination proceeding, or supplemental examination proceeding, a patent owner who was not the applicant under 37 CFR 1.46 must appoint any power of attorney in compliance with 37 CFR 3.71 and 3.73. See 37 CFR 1.32(b)(4).

/lqchau/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/577,227	12/19/2014	Patricia Allison Tewes Richards	091856-0158

22428  
 Foley & Lardner LLP  
 3000 K STREET N.W.  
 SUITE 600  
 WASHINGTON, DC 20007-5109

**CONFIRMATION NO. 5836**  
**IMPROPER CFR REQUEST**



Date Mailed: 08/18/2015

## RESPONSE TO REQUEST FOR CORRECTED FILING RECEIPT

### *Power of Attorney, Claims, Fees, System Limitations, and Miscellaneous*

In response to your request for a corrected Filing Receipt, the Office is unable to comply with your request because:

- Any request to correct or update the name of the applicant must include an application data sheet (ADS) in compliance with 37 CFR 1.76 specifying the correct or updated name of the applicant in the applicant information section. Any request to change the applicant after an original applicant has been specified under 37 CFR 1.46(b) must include a new ADS in compliance with 37 CFR 1.76 specifying the applicant in the applicant information section and comply with 37 CFR 3.71 and 3.73. See 37 CFR 1.46(c).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/lqchau/



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 Alexandria, Virginia 22313-1450  
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/577,227	12/19/2014	Patricia Allison Tewes Richards	091856-0158	5836

22428 7590 08/25/2015  
 Foley & Lardner LLP  
 3000 K STREET N.W.  
 SUITE 600  
 WASHINGTON, DC 20007-5109

EXAMINER
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KANTAMNENI, SHOBHA

ART UNIT	PAPER NUMBER
----------	--------------

1627

NOTIFICATION DATE	DELIVERY MODE
-------------------	---------------

08/25/2015

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipdocketing@foley.com

**Office Action Summary**Application No.  
14/577,227Applicant(s)  
RICHARDS, PATRICIA ALLISON  
TEWESExaminer  
SHOBHA KANTAMNENIArt Unit  
1627AIA (First Inventor to File)  
Status  
No**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --****Period for Reply**A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_\_.  
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on \_\_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on \_\_\_\_\_; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims\***

- 5) ☒ Claim(s) 13-26 is/are pending in the application.  
5a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 6) ☒ Claim(s) NONE is/are allowed.
- 7) ☒ Claim(s) 13-26 is/are rejected.
- 8) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 9) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

\* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see [http://www.uspto.gov/patents/init\\_events/pph/index.jsp](http://www.uspto.gov/patents/init_events/pph/index.jsp) or send an inquiry to [PPHfeedback@uspto.gov](mailto:PPHfeedback@uspto.gov).

**Application Papers**

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

- a) ☐ All b) ☐ Some\*\* c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\*\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)  
Paper No(s)/Mail Date 08/07/2015.
- 3) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 4) ☐ Other: \_\_\_\_\_.

Application/Control Number: 14/577,227  
Art Unit: 1627

Page 2

The present application is being examined under the pre-AIA first to invent provisions.

### **DETAILED ACTION**

Claims 13-26 are pending and examined herein.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 13-26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of US patent No. 8,658,663, in view of Gould (International Journal of Pharmaceutics, 33 1986, pages 201-217, PTO-892 of record in the '663). Although the conflicting claims are not identical, they are obvious over each other. Instant claims are drawn to a method of treating a patient suffering from thermoregulatory dysfunction comprising administering paroxetine or pharmaceutically acceptable salt of paroxetine in an amount of 7.5 mg/day based on paroxetine moiety and the stated claims 1-5 of US patent No.

Application/Control Number: 14/577,227

Page 3

Art Unit: 1627

8,658,663 are drawn to a method of treating a patient suffering from thermoregulatory dysfunction comprising administering paroxetine mesylate in an amount of 7.5 mg/day based on paroxetine moiety.

Gould teaches that salt form of drugs provide the means of altering the physicochemical properties such as aqueous solubility, stability and biological characteristics of a drug without altering its chemical structure. It is also taught that hydrochloride salts, mesylate salts and other salts of basic drugs are all FDA-approved commercially marketed salts of anionic salt-forming species. See abstract; page 202 TABLE 1.

It would have been obvious to a person of ordinary skill in the art at the time of invention to employ hydrochloride, sulfate, bisulfate or phosphates salts of paroxetine to treat thermoregulatory dysfunction associated with menopause because Gould teaches that salt form of drugs provide the means of altering the physicochemical properties such as aqueous solubility, stability and biological characteristics of a drug without altering its chemical structure, and further teaches that hydrochloride salts, mesylate salts and other salts of basic drugs are all FDA-approved commercially marketed salts of anionic salt-forming species. One of ordinary skill in the art would have been motivated at the time of invention to use hydrochloride salt, mesylate salts or other salts of paroxetine with the expectation of obtaining a pharmaceutical composition with better physicochemical properties such as aqueous solubility, stability and biological characteristics of paroxetine, and useful for treating a patient suffering from thermoregulatory dysfunction.

Application/Control Number: 14/577,227  
Art Unit: 1627

Page 4

Thus, instant claims are obvious over claims 1-5 of US patent No. 8,658,663.

Claims 13-26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of US Patent No. 8,859,576, in view of Gould (International Journal of Pharmaceutics, 33 1986, pages 201-217, PTO-892 of record in the '663). Although the conflicting claims are not identical, they are obvious over each other because the subject matter which is drawn to a method of treating a patient suffering from thermoregulatory dysfunction comprising administering a dosage form of paroxetine or pharmaceutically acceptable salt of paroxetine in an amount of 7.5 mg/day based on paroxetine moiety embraced in the instant claims overlaps with the stated claims 1-5 of US Patent No. 8,859,576 which is drawn to a method of treating a patient suffering from thermoregulatory dysfunction comprising administering paroxetine hydrochloride in an amount of 7.5 mg/day based on paroxetine moiety. The claimed method is within the scope of the claims 1-5 of US Patent No. 8,859,576.

Gould teaches that salt form of drugs provide the means of altering the physicochemical properties such as aqueous solubility, stability and biological characteristics of a drug without altering its chemical structure. It is also taught that hydrochloride salts, mesylate salts and other salts of basic drugs are all FDA-approved commercially marketed salts of anionic salt-forming species. See abstract; page 202 TABLE 1.

Application/Control Number: 14/577,227

Page 5

Art Unit: 1627

Further, it would have been obvious to a person of ordinary skill in the art at the time of invention to employ sulfate, bisulfate or phosphates salts of paroxetine to treat thermoregulatory dysfunction associated with menopause because Gould teaches that salt form of drugs provide the means of altering the physiocochemical properties such as aqueous solubility, stability and biological characteristics of a drug without altering its chemical structure, and further teaches that hydrochloride salts, mesylate salts and other salts of basic drugs are all FDA-approved commercially marketed salts of anionic salt-forming species. One of ordinary skill in the art would have been motivated at the time of invention to use other salts of paroxetine with the expectation of obtaining a pharmaceutical composition with better physiocochemical properties such as aqueous solubility, stability and biological characteristics of paroxetine, and useful for treating a patient suffering from thermoregulatory dysfunction.

Thus, instant claims and claims of US Patent No. 8,859,576 are obvious over each other.

Claims 19, 21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of US Patent No. 8,946,251, in view of Gould (International Journal of Pharmaceutics, 33 1986, pages 201-217, PTO-892 of record in the '663). Although the conflicting claims are not identical, they are obvious over each other because the subject matter which is drawn to a method of treating a patient suffering from thermoregulatory dysfunction comprising administering a dosage form comprises paroxetine hydrochloride or paroxetine

Application/Control Number: 14/577,227

Page 6

Art Unit: 1627

mesylate in an amount of 7.5 mg/day based on paroxetine moiety embraced in the instant claims overlaps with the stated claims 1-12 of US Patent No. 8,946,251 which is drawn to a method of treating a patient suffering from thermoregulatory dysfunction comprising administering paroxetine in a dosage form comprising paroxetine or a pharmaceutically acceptable salt such as hydrochloride salt in an amount of 7.5 mg/day based on paroxetine moiety. The claimed method is within the scope of the claims 1-12 of US Patent No. 8,946,251.

Gould teaches that salt form of drugs provide the means of altering the physicochemical properties such as aqueous solubility, stability and biological characteristics of a drug without altering its chemical structure. It is also taught that hydrochloride salts, mesylate salts and other salts of basic drugs are all FDA-approved commercially marketed salts of anionic salt-forming species. See abstract; page 202 TABLE 1.

Further, it would have been obvious to a person of ordinary skill in the art at the time of invention to employ mesylate salt of paroxetine to treat thermoregulatory dysfunction associated with menopause because Gould teaches that salt form of drugs provide the means of altering the physicochemical properties such as aqueous solubility, stability and biological characteristics of a drug without altering its chemical structure, and further teaches that hydrochloride salts, mesylate salts and other salts of basic drugs are all FDA-approved commercially marketed salts of anionic salt-forming species. One of ordinary skill in the art would have been motivated at the time of invention to use other salts of paroxetine with the expectation of obtaining a pharmaceutical composition

Application/Control Number: 14/577,227

Page 7

Art Unit: 1627

with better physiocochemical properties such as aqueous solubility, stability and biological characteristics of paroxetine, and useful for treating a patient suffering from thermoregulatory dysfunction.

Thus, instant claims and claims of US Patent No. 8,859,576 are obvious over each other.

### ***Double Patenting***

A rejection based on double patenting of the “same invention” type finds its support in the language of 35 U.S.C. 101 which states that “whoever invents or discovers any new and useful process... may obtain a patent therefor...” (Emphasis added). Thus, the term “same invention,” in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the claims that are directed to the same invention so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 13-18, 20, 22-26 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-12 of prior U.S. Patent No. 8,946,251. This is a statutory double patenting rejection.

Application/Control Number: 14/577,227  
Art Unit: 1627

Page 8

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shobha Kantamneni, Ph.D  
Patent Examiner  
Art Unit : 1627

/SHOBHA KANTAMNENI/

Examiner, Art Unit 1627

**Index of Claims**

Application/Control No.

14/577,227

Applicant(s)/Patent under  
ReexaminationRICHARDS, PATRICIA  
ALLISON TEWES

Examiner

SHOBHA KANTAMNENI

Art Unit

1627

√	Rejected
=	Allowed

—	(Through numeral) Cancelled
÷	Restricted

N	Non-Elected
I	Interference

A	Appeal
O	Objected

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<b>Search Notes</b>  	<b>Application/Control No.</b>  14577227	<b>Applicant(s)/Patent Under Reexamination</b>  RICHARDS, PATRICIA ALLISON TEWES
	<b>Examiner</b>  SHOBHA KANTAMNENI	<b>Art Unit</b>  1627

CPC- SEARCHED		
Symbol	Date	Examiner
A61K 31/4525	8/19/2015	ks

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search done on PALM	8/19/2015	ks
EAST, NPL search done	8/19/2015	ks

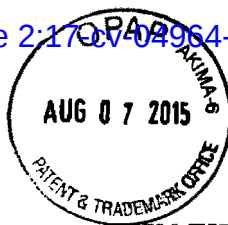
INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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**EAST Search History****EAST Search History (Prior Art)**

<b>Ref #</b>	<b>Hits</b>	<b>Search Query</b>	<b>DBs</b>	<b>Default Operator</b>	<b>Plurals</b>	<b>Time Stamp</b>
L9	23165	"S74"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/08/19 14:54
L10	17758	"S67"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/08/19 14:55
L11	13439	paroxetine	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/08/19 14:55
L12	4329	"hot flashes"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/08/19 14:56
L13	2428	"hot flushes"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/08/19 14:56
L14	6174	L12 or L13	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/08/19 14:56
L15	841	L11 and L14	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/08/19 14:56
L16	7988	A61K31/4525	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/08/19 14:57
L17	14887	C07D211/22	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/08/19 14:57
L18	437	C07D317/06	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/08/19 14:57

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Atty. Dkt. No. 091856-0158

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

First Inventor Name: Patricia Allison Tewes RICHARDS

Title: Method of Treating Thermoregulatory  
Dysfunction with Paroxetine

Appl. No.: 14/577227

Filing Date: 12/19/2014

Examiner: Unassigned

Art Unit: 1629

Confirmation Number: 5836

**INFORMATION DISCLOSURE STATEMENT**  
**UNDER 37 CFR §1.56**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicant respectfully requests that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

Applicant requests that, in accordance with 37 CFR §1.98(d), the Examiner review all applications relied on for an earlier effective filing date under 35 U.S.C. 120, including Application No. 11/499,586, filed 8/4/2006; Application No. 12/292,960, filed 12/1/2008; and Application No. 14/157,992, filed 1/17/2014, for copies of references of record therein that are

Atty. Dkt. No. 091856-0158

not being provided here. Applicant would be pleased to provide copies of any such documents at the Examiner's request.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicant does not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

#### **TIMING OF THE DISCLOSURE**

The listed documents are being submitted in compliance with 37 CFR §1.97(b), before the mailing date of the first Office Action on the merits.

#### **RELEVANCE OF LISTED DOCUMENTS**

Documents A1-A2 are granted parent patents. Document A3 is granted sister patent filed as a continuation of Document A2. Document A4 is the published version of U.S. Application No. 11/499,586, to which this application and Documents A1-A3 claim priority.

Documents A15, A43, A49, A56-A58, A60, A64-A65, A67-A69, A85, and A87-A94, were cited by a third party as relevant to the validity of Document A2.

Documents A101 and A102 were cited during prosecution of the corresponding Japanese application. An English-language abstract is submitted for Document A101. An English-language abstract is not available for Document A102, however, Applicant provides the following concise explanation of relevance pursuant to MPEP 609.04(a):

The Japanese Office Action cited Document A102 to support the statement that "it was known at the effective date of the present application that the "thermoregulatory dysfunction" may be caused by numerous diseases such as neural diseases, e.g., autonomic disorder by spinal damage."

Atty. Dkt. No. 091856-0158

Applicant therefore respectfully requests consideration of all cited references,

Although Applicant believes that no fee is required, the Commissioner is hereby authorized to charge any additional fees which may be due to Deposit Account No. 19-0741.

Respectfully submitted,

Date August 5, 2015

By Courtenay C. Brinckerhoff

FOLEY & LARDNER LLP  
Customer Number: 22428  
Telephone: (202) 295-4094  
Facsimile: (202) 672-5399

Courtenay C. Brinckerhoff  
Attorney for Applicant  
Registration No. 37,288

AUG 07 2015

PTO/SB/08 (09-06)

Approved for use through 03/31/2007. OMB 0651-0031

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO		<b>Complete if Known</b>	
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>		<b>Application Number</b>	14/577,227
		<b>Filing Date</b>	12/19/2014
Date Submitted: August 7, 2015 (use as many sheets as necessary)		<b>First Named Inventor</b>	Joel S. Lippman
		<b>Art Unit</b>	1629
Sheet 1 of 6		<b>Examiner Name</b>	Unassigned
		<b>Attorney Docket Number</b>	091856-0158

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. <sup>1</sup>	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code <sup>2</sup> (if known)			
/S.K./	A1	US-8,946,251	02/03/2015	RICHARDS	
/S.K./	A2	US-8,658,663	02/25/2014	RICHARDS	
/S.K./	A3	US-8,859,576	10/14/2014	RICHARDS	
/S.K./	A4	US-2008/0033050	02/07/2008	RICHARDS	
/S.K./	A5	US-4,007,196	2/8/1977	CHRISTENSEN, ET AL.	
/S.K./	A6	US-4,721,723	1/26/1988	BARNES, ET AL.	
/S.K./	A7	US-4,861,893	8/29/1989	BARRETT,	
/S.K./	A8	US-5,039,803	8/13/1991	SMITH, ET AL.	
/S.K./	A9	US-5,470,846	11/28/1995	SANDYK	
/S.K./	A10	US-5,672,612	9/30/1997	ROSEN, ET AL.	
/S.K./	A11	US-5,872,132	2/16/1999	WARD, ET AL.	
/S.K./	A12	US-5,900,423	5/4/1999	WARD, ET AL.	
/S.K./	A13	US-5,955,475	9/21/1999	KRAPE, ET AL.	
/S.K./	A14	US-5,985,322	11/16/1999	ANDERSEN, ET AL.	
/S.K./	A15	US-6,063,927	5/16/2000	CRAIG, ET AL.	
/S.K./	A16	US-6,080,759	6/27/2000	WARD, ET AL.	
/S.K./	A17	US-6,113,944	9/5/2000	PATHAK, ET AL.	
/S.K./	A18	US-6,133,277	10/17/2000	WIGERNICK, ET AL.	
/S.K./	A19	US-6,172,233	1/9/2001	WARD	
/S.K./	A20	US-6,326,496	12/4/2001	BRENNAN	
/S.K./	A21	US-6,369,051	4/9/2002	JENKINS	
/S.K./	A22	US-6,433,179	8/13/2002	WANG, ET AL.	
/S.K./	A23	US-6,436,956	8/20/2002	MURTHY, ET AL.	
/S.K./	A24	US-6,440,459	8/27/2002	STMPA DIX DEL CORRAL, ET AL.	
/S.K./	A25	US-6,498,184	12/24/2002	BERENDSEN	
/S.K./	A26	US-6,541,637	4/1/2003	OKATAKE, ET AL.	
/S.K./	A27	US-6,645,523	11/11/2003	LEMMENS, ET AL.	
/S.K./	A28	US-6,660,298	12/9/2003	ROSEN, ET AL.	
/S.K./	A29	US-6,686,473	2/3/2004	LEMMENS, ET AL.	
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		<b>Filing Date</b>	12/19/2014
		<b>First Named Inventor</b>	Joel S. Lippman
		<b>Art Unit</b>	1629
		<b>Examiner Name</b>	Unassigned
<b>Sheet</b>	2	<b>of</b>	6
		<b>Attorney Docket Number</b>	091856-0158

U.S. PATENT DOCUMENTS					
Examiner	Cite No. <sup>1</sup>	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where
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/S.K./	A50	US-2008/0254073	10/16/2008	CHI	

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS					
Examiner Initials*	Cite No. <sup>1</sup>	U.S. Patent Application Document Serial Number-Kind Code <sup>2</sup> (if known)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. <sup>1</sup>	Foreign Patent Document Country Code* Number <sup>4</sup> Kind Code <sup>5</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T <sup>6</sup>
/S.K./	A51	WO 99/44601 *	9/10/1999	ELI LILLY AND COMPANY		
/S.K./	A52	WO 99/47519 *	09/23/1999	SMITHKLINE BEECHAM PLC		
/S.K./	A53	WO 99/56751 *	11/11/1999	ENDO PHARMACEUTICALS INC.		
/S.K./	A54	WO 00/78291 *	12/28/2000	SMITHKLINE BEECHAM PLC		
/S.K./	A55	WO 2007/043057 *	04/19/2007	YISSUM, RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM		
/S.K./	A56	WO 02/100404 A2 ✓	12/19/2002	PANTERHEI BIOSCIENCE B.V.		
/S.K./	A57	WO 2004/035058 A1 ✓	04/29/2004	WYETH		

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/S.K./	A58	Berendsen, "The Role of Serotonin in Hot Flushes," 36 Maturitas 155 (2000) ✓	

Examiner Signature	/Shobha Kantamneni/	Date Considered	08/19/2015
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4842-8805-7638.1

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		Filing Date	12/19/2014
		First Named Inventor	Joel S. Lippman
		Art Unit	1629
		Examiner Name	Unassigned
Sheet	3	of	6
		Attorney Docket Number	091856-0158

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>6</sup>
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		First Named Inventor	Joel S. Lippman
		Art Unit	1629
		Examiner Name	Unassigned
Sheet 4 of 6	Attorney Docket Number	091856-0158	

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		Art Unit	1629
		Examiner Name	Unassigned
Sheet	5	of	6
		Attorney Docket Number	091856-0158

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/S.K./	A101	YAGUCHI ET AL., "Rehabilitation Difficulties in a Patient with a Thermoregulation Disturbance due to Striatonigral Degeneration," Japan J. Rehabil. Med., Vol. 41, No. 1, pp. 48-51, (January 18, 2004). ✓	ABS.
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/577,227	12/19/2014	Patricia Allison Tewes Richards	091856-0158

CONFIRMATION NO. 5836

## PUBLICATION NOTICE



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22428  
 Foley & Lardner LLP  
 3000 K STREET N.W.  
 SUITE 600  
 WASHINGTON, DC 20007-5109

**Title:**METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE

**Publication No.**US-2015-0335631-A1

**Publication Date:**11/26/2015

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The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

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Atty. Dkt. No 091856-0158

***IN THE UNITED STATES PATENT AND TRADEMARK OFFICE***

First Inventor Name: Patricia Allison Tewes RICHARDS  
Title: Method of Treating Thermoregulatory  
Dysfunction with Paroxetine  
Appl. No.: 14/577227  
Filing Date: 12/19/2014  
Examiner: Unassigned  
Art Unit: 1629  
Confirmation Number: 5836

**TRANSMITTAL OF SECOND APPLICATION DATA SHEET AND REQUEST FOR  
CORRECTED FILING RECEIPT**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Commissioner:

Attached is a Second Application Data Sheet for the captioned application.

The Second Application Data Sheet is being submitted in compliance with 37 CFR 1.76 to update the name of the Applicant to the Assignee: NOVEN THERAPEUTICS, LLC, and to update the residence and address of the inventor. These updates have been marked by strikethrough and underlining on the Second Application Data Sheet.

Applicant respectfully requests that a Corrected Filing Receipt be issued to reflect the updated Applicant and inventor information.

Atty. Dkt. No 091856-0158

Although Applicant believes no fee is due, the Commissioner is authorized to charge deposit account number 19-0741 for any required fees.

Respectfully submitted,

Date Feb 16, 2016

FOLEY & LARDNER LLP  
Customer Number: 22428  
Telephone: (202) 295-4094  
Facsimile: (202) 672-5399

By Courtenay C. Brinckerhoff

Courtenay C. Brinckerhoff  
Attorney for Applicant  
Registration No. 37,288

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	091856-0158
		Application Number	
Title of Invention	Method of Treating Thermoregulatory Dysfunction with Paroxetine		
<p>The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.</p> <p>This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.</p>			

**Secrecy Order 37 CFR 5.2**

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2. (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

**Inventor Information:**

Inventor 1 <span style="float: right;">Remove</span>				
Legal Name				
Prefix	Given Name	Middle Name	Family Name	Suffix
	Patricia	Allison Tewes	RICHARDS	
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service				
City	<del>Scarsdale</del> Bradenton	State/Province	<del>NY</del> FL	Country of Residence
				US
Mailing Address of Inventor:				
Address 1	448 Edgemont Road 3212 Bay Drive			
Address 2				
City	<del>Scarsdale</del> Bradenton	State/Province	<del>NY</del> FL	
Postal Code	<del>10583</del> 34207	Country	US	
All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button. <span style="float: right;">Add</span>				

**Correspondence Information:**

Enter either Customer Number or complete the Correspondence Information section below.  
For further information see 37 CFR 1.33(a).

☐ An Address is being provided for the correspondence information of this application.

Customer Number	22428		
Email Address	IPDocketing@foley.com	Add Email	Remove Email

**Application Information:**

Title of the Invention	Method of Treating Thermoregulatory Dysfunction with Paroxetine		
Attorney Docket Number	091856-0158	Small Entity Status Claimed <input type="checkbox"/>	
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	0	Suggested Figure for Publication (if any)	n/a

**Filing By Reference :**

<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	091856-0158
		Application Number	
Title of Invention	Method of Treating Thermoregulatory Dysfunction with Paroxetine		

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

### Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

### Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	<input checked="" type="radio"/> Customer Number	<input type="radio"/> US Patent Practitioner	<input type="radio"/> Limited Recognition (37 CFR 11.9)
Customer Number	22428		

### Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the application number blank.

Prior Application Status		<a href="#">Remove</a>	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	14/157992	2014-01-17
Prior Application Status		<a href="#">Remove</a>	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
14/157992	Continuation of	12/292960	2008-12-01
Prior Application Status		<a href="#">Remove</a>	

<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	091856-0158
		Application Number	
Title of Invention	Method of Treating Thermoregulatory Dysfunction with Paroxetine		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12/292960	Continuation of	11/499586	2006-08-04
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the <b>Add</b> button.			

### Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)<sup>i</sup> the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			<a href="#">Remove</a>
Application Number	Country <sup>i</sup>	Filing Date (YYYY-MM-DD)	Access Code <sup>j</sup> (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the <b>Add</b> button.			

### Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

<p>This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.</p> <p><input type="checkbox"/> NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.</p>
--

### Authorization to Permit Access:

<input checked="" type="checkbox"/> Authorization to Permit Access to the Instant Application by the Participating Offices
--

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	091856-0158
		Application Number	
Title of Invention	Method of Treating Thermoregulatory Dysfunction with Paroxetine		

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

## Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

### Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

☒ Assignee
 ☐ Legal Representative under 35 U.S.C. 117
 ☐ Joint Inventor

☐ Person to whom the inventor is obligated to assign.
 ☐ Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name NOVEN THERAPEUTICS, LLC

### Mailing Address Information For Applicant:

Address 1 11960 Southwest 144th Street

Address 2

City Miami

State/Province

FL

Country US

Postal Code

33186

Phone Number

Fax Number

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

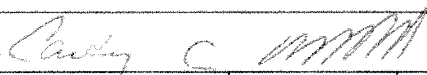
<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	091856-0158
		Application Number	
Title of Invention	Method of Treating Thermoregulatory Dysfunction with Paroxetine		
Email Address			
Additional Applicant Data may be generated within this form by selecting the Add button.			

**Assignee Information including Non-Applicant Assignee Information:**

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

<b>Assignee 1</b>			
Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.			
If the Assignee or Non-Applicant Assignee is an Organization check here. <input checked="" type="checkbox"/>			
Organization Name	NOVEN THERAPEUTICS, LLC		
<b>Mailing Address Information For Assignee including Non-Applicant Assignee:</b>			
Address 1	11960 Southwest 144th Street		
Address 2			
City	Miami	State/Province	FL
Country	US	Postal Code	33186
Phone Number		Fax Number	
Email Address			
Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.			

**Signature:**

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications.					
Signature				Date (YYYY-MM-DD)	20160216
First Name	Courtenay C.	Last Name	Brinckerhoff	Registration Number	37288
Additional Signature may be generated within this form by selecting the Add button.					

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	091856-0158
		Application Number	
Title of Invention	Method of Treating Thermoregulatory Dysfunction with Paroxetine		

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

PTO/AIA/96 (08-12)

Approved for use through 01/31/2013. OMB 0651-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**STATEMENT UNDER 37 CFR 3.73(c)**Applicant/Patent Owner: Patricia Allison Tewes RichardsApplication No./Patent No.: 14/577227 Filed/Issue Date: 12/19/2014Titled: Method of Treating Thermoregulatory Dysfunction with ParoxetineNOVEN THERAPEUTICS, LLC, a Corporation

(Name of Assignee)

(Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose one of options 1, 2, 3 or 4 below):

1. ☒ The assignee of the entire right, title, and interest.
2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):
- ☐ The extent (by percentage) of its ownership interest is \_\_\_\_\_%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.
- ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (e.g., bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose one of options A or B below):

- A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel \_\_\_\_\_, Frame \_\_\_\_\_, or for which a copy thereof is attached.
- B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Patricia Allison Tewes Richards To: JDS Pharmaceuticals, LLCThe document was recorded in the United States Patent and Trademark Office at  
Reel 018388, Frame 0706, or for which a copy thereof is attached.2. From: JDS Pharmaceuticals, LLC To: Noven Therapeutics, LLCThe document was recorded in the United States Patent and Trademark Office at  
Reel 020565, Frame 0921, or for which a copy thereof is attached.

[Page 1 of 2]

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

'237 FH -0185

PTO/AIA/96 (08-12)

Approved for use through 01/31/2013. OMB 0651-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**STATEMENT UNDER 37 CFR 3.73(c)**

3. From: \_\_\_\_\_ To: \_\_\_\_\_

The document was recorded in the United States Patent and Trademark Office at  
Reel \_\_\_\_\_, Frame \_\_\_\_\_, or for which a copy thereof is attached.

4. From: \_\_\_\_\_ To: \_\_\_\_\_

The document was recorded in the United States Patent and Trademark Office at  
Reel \_\_\_\_\_, Frame \_\_\_\_\_, or for which a copy thereof is attached.

5. From: \_\_\_\_\_ To: \_\_\_\_\_


The document was recorded in the United States Patent and Trademark Office at  
Reel \_\_\_\_\_, Frame \_\_\_\_\_, or for which a copy thereof is attached.

6. From: \_\_\_\_\_ To: \_\_\_\_\_

The document was recorded in the United States Patent and Trademark Office at  
Reel \_\_\_\_\_, Frame \_\_\_\_\_, or for which a copy thereof is attached.☐ Additional documents in the chain of title are listed on a supplemental sheet(s).☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

  
Signature

Courtenay C. Brinckerhoff

Printed or Typed Name

Feb 16, 2016  
Date

37,288

Title or Registration Number

PTO/AIA/80 (97-12)

Approved for use through 11/30/2014. OMB 0651-0035

U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO**

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:



Practitioners associated with Customer Number

22428

OR



Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number

Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignments documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:



The address associated with Customer Number:

22428

OR

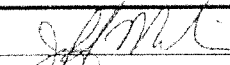
<input type="checkbox"/> Firm or Individual Name		
Address		
City		
Country		
Telephone		Email

Assignee Name and Address: NOVEN THERAPEUTICS, LLC  
 11960 Southwest 144th Street  
 Miami, Florida 33186

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of The practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

**SIGNATURE of Assignee of Record**

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date	5-16-14
Name	Jeff Munn	Telephone	(305) 253-5099
Title	Manager		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

**Electronic Acknowledgement Receipt**

<b>EFS ID:</b>	24926786
<b>Application Number:</b>	14577227
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	5836
<b>Title of Invention:</b>	METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE
<b>First Named Inventor/Applicant Name:</b>	Patricia Allison Tewes Richards
<b>Customer Number:</b>	22428
<b>Filer:</b>	Courtenay C. Brinckerhoff
<b>Filer Authorized By:</b>	
<b>Attorney Docket Number:</b>	091856-0158
<b>Receipt Date:</b>	16-FEB-2016
<b>Filing Date:</b>	19-DEC-2014
<b>Time Stamp:</b>	17:08:23
<b>Application Type:</b>	Utility under 35 USC 111(a)

**Payment information:**

Submitted with Payment		no			
<b>File Listing:</b>					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		poa.pdf	917959 21a849eff21cfdc1e362cbb6861d22b80cc5698	yes	11

## Multipart Description/PDF files in .zip description

	Document Description	Start	End
	Request for Corrected Filing Receipt	1	2
	Application Data Sheet	3	8
	Assignee showing of ownership per 37 CFR 3.73	9	10
	Power of Attorney	11	11

**Warnings:****Information:**

<b>Total Files Size (in bytes):</b>	917959
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**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**

**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**



## UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
 United States Patent and Trademark Office  
 Address: COMMISSIONER FOR PATENTS  
 P.O. Box 1450  
 Alexandria, Virginia 22313-1450  
 www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/577,227	12/19/2014	Patricia Allison Tewes Richards	091856-0158

22428  
 Foley & Lardner LLP  
 3000 K STREET N.W.  
 SUITE 600  
 WASHINGTON, DC 20007-5109

**CONFIRMATION NO. 5836**  
**POA ACCEPTANCE LETTER**



Date Mailed: 02/23/2016

### NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 02/16/2016.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/byemane/



## UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
 United States Patent and Trademark Office  
 Address: COMMISSIONER FOR PATENTS  
 P.O. Box 1450  
 Alexandria, Virginia 22313-1450  
 www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
14/577,227	12/19/2014	1627	1740	091856-0158	14	1

CONFIRMATION NO. 5836

CORRECTED FILING RECEIPT



CC000000080785671

22428

Foley & Lardner LLP  
 3000 K STREET N.W.  
 SUITE 600  
 WASHINGTON, DC 20007-5109

Date Mailed: 02/23/2016

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

**Inventor(s)**

Patricia Allison Tewes Richards, Scarsdale, NY;

**Applicant(s)**

NOVEN THERAPEUTICS, LLC, Miami, FL;

**Assignment For Published Patent Application**

Noven Therapeutics, LLC, Miami, FL

**Power of Attorney:** The patent practitioners associated with Customer Number 22428**Domestic Priority data as claimed by applicant**

This application is a CON of 14/157,992 01/17/2014 PAT 8946251  
 which is a CON of 12/292,960 12/01/2008 PAT 8658663  
 which is a CON of 11/499,586 08/04/2006 ABN

**Foreign Applications** for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

*Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.*

**Permission to Access Application via Priority Document Exchange:** Yes**Permission to Access Search Results:** No

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

**If Required, Foreign Filing License Granted:** 01/08/2015

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/577,227**

**Projected Publication Date:** Not Applicable

**Non-Publication Request:** No

**Early Publication Request:** No

**Title**

METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE

**Preliminary Class**

514

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

## **PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES**

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

## **LICENSE FOR FOREIGN FILING UNDER**

### **Title 35, United States Code, Section 184**

### **Title 37, Code of Federal Regulations, 5.11 & 5.15**

#### **GRANTED**

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

#### **NOT GRANTED**

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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### ***SelectUSA***

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit <http://www.SelectUSA.gov> or call +1-202-482-6800.

Doc Code: DIST.E.FILE

Document Description: Electronic Terminal Disclaimer - Filed

U.S. Patent and Trademark Office  
Department of Commerce

Electronic Petition Request	<b>TERMINAL DISCLAIMER TO OBIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT</b>
Application Number	14577227
Filing Date	19-Dec-2014
First Named Inventor	Patricia Richards
Attorney Docket Number	091856-0158
Title of Invention	METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
NOVEN THERAPEUTICS, LLC	100%

The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

8658663

8859576

8946251

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:

- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

- ☒ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.
- ☐ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

Applicant claims the following fee status:

- ☐ Small Entity
- ☐ Micro Entity
- ☒ Regular Undiscounted

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

- ☒ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application
- Registration Number 37288
- ☐ A sole inventor
- ☐ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application
- ☐ A joint inventor; all of whom are signing this request

Signature	/Courtenay C. Brinckerhoff/
Name	Courtenay C Brinckerhoff

\*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).  
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal				
<b>Application Number:</b>		14577227		
<b>Filing Date:</b>		19-Dec-2014		
<b>Title of Invention:</b>		METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE		
<b>First Named Inventor/Applicant Name:</b>		Patricia Allison Tewes Richards		
<b>Filer:</b>		Courtenay C. Brinckerhoff/Christine Arthur		
<b>Attorney Docket Number:</b>		091856-0158		
Filed as Large Entity				
<b>Filing Fees for Utility under 35 USC 111(a)</b>				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
<b>Basic Filing:</b>				
Statutory or Terminal Disclaimer	1814	1	160	160
<b>Pages:</b>				
<b>Claims:</b>				
<b>Miscellaneous-Filing:</b>				
<b>Petition:</b>				
<b>Patent-Appeals-and-Interference:</b>				
<b>Post-Allowance-and-Post-Issuance:</b>				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				160

Doc Code: DISQ.E.FILE

Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 14577227

Filing Date: 19-Dec-2014

Applicant/Patent under Reexamination: Richards et al.

Electronic Terminal Disclaimer filed on February 24, 2016

☒ APPROVED

**This patent is subject to a terminal disclaimer**

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

**Electronic Acknowledgement Receipt**

<b>EFS ID:</b>	24997435
<b>Application Number:</b>	14577227
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	5836
<b>Title of Invention:</b>	METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE
<b>First Named Inventor/Applicant Name:</b>	Patricia Allison Tewes Richards
<b>Customer Number:</b>	22428
<b>Filer:</b>	Courtenay C. Brinckerhoff/Christine Arthur
<b>Filer Authorized By:</b>	Courtenay C. Brinckerhoff
<b>Attorney Docket Number:</b>	091856-0158
<b>Receipt Date:</b>	24-FEB-2016
<b>Filing Date:</b>	19-DEC-2014
<b>Time Stamp:</b>	11:20:31
<b>Application Type:</b>	Utility under 35 USC 111(a)

**Payment information:**

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	\$160
RAM confirmation Number	11162
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

**'237 FH -0199**

**File Listing:**

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Electronic Terminal Disclaimer-Filed	eTerminal-Disclaimer.pdf	34027	no	2
			108ea325cb9aa2dd02e5348f9a0ac354828 416be		

**Warnings:****Information:**

2	Fee Worksheet (SB06)	fee-info.pdf	30865	no	2
			98ae23dace47f8b2392f65d04cc62d3d773 78053		

**Warnings:****Information:**

<b>Total Files Size (in bytes):</b>			64892
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Atty. Dkt. No. 091856-0158

***IN THE UNITED STATES PATENT AND TRADEMARK OFFICE***

First Inventor Name: Patricia Allison Tewes RICHARDS  
Title: Method of Treating Thermoregulatory Dysfunction  
with Paroxetine  
Appl. No.: 14/577,227  
Filing Date: 12/19/2014  
Examiner: KANTAMNENI  
Art Unit: 1629  
Confirmation Number: 5836

**AMENDMENT AND REPLY UNDER 37 CFR 1.111**

Mail Stop AMENDMENT  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Commissioner:

This is a reply to the non-final Office Action mailed August 25, 2015. Applicant hereby petitions for an extension of time to make this response timely. The Commissioner is hereby authorized to charge any additional fees which may be required for this application to Deposit Account No. 19-0741.

**Amendments to the Claims** are reflected in the listing of claims which begins on page 2.

**Remarks/Arguments** begin on page 4.

Please amend the application as follows:

Atty. Dkt. No. 091856-0158

**Amendments to the Claims:**

This listing of claims will replace all prior versions and listings of claims in the application:

**Listing of Claims:**

Claims 1-12 (Canceled)

13. (Currently Amended) A method for treating a female patient suffering from thermoregulatory dysfunction associated with menopause, ~~comprising~~ consisting of administering a dosage form of paroxetine to said patient in an amount, based on the paroxetine moiety, of 7.5 mg/day.

14. (Previously Presented) The method of claim 13, wherein said thermoregulatory dysfunction is a condition selected from the group consisting of hot flashes, hot flushes, night sweats, and combinations thereof.

15. (Previously Presented) The method of claim 13, wherein said dosage form comprises paroxetine free base.

16. (Previously Presented) The method of claim 13, wherein said dosage form comprises a pharmaceutically acceptable salt of paroxetine.

17. (Previously Presented) The method of claim 13, wherein said dosage form comprises a pharmaceutically acceptable salt of paroxetine selected from the group consisting of hydrohalides, sulfates, phosphates, oxalate, tosylate, pamoate, citrate, carbonate, bicarbonate, maleate, malate, and fumarate.

18. (Previously Presented) The method of claim 13, wherein said dosage form comprises a

Atty. Dkt. No. 091856-0158

pharmaceutically acceptable salt of paroxetine selected from the group consisting of hydrochloride, hydrobromide, and hydroiodide, and combinations of two or more thereof.

19. (Previously Presented) The method of claim 13, wherein said dosage form comprises paroxetine hydrochloride.

20. (Previously Presented) The method of claim 13, wherein said dosage form comprises a pharmaceutically acceptable salt of paroxetine selected from the group consisting of sulfate and bisulfate, and combinations thereof.

21. (Previously Presented) The method of claim 13, wherein said dosage form comprises paroxetine mesylate.

22. (Previously Presented) The method of claim 13, wherein said dosage form comprises a pharmaceutically acceptable salt of paroxetine selected from the group consisting of mono, di, and tri basic phosphates, and combinations of two or more thereof.

23. (Previously Presented) The method of claim 13, wherein said dosage form comprises paroxetine or a pharmaceutically acceptable salt thereof in anhydrate, hydrate, or solvate form, or a combination of two or more thereof.

24. (Previously Presented) The method of claim 13, wherein said dosage form comprises paroxetine or a pharmaceutically acceptable salt thereof in a crystalline or amorphous form, or a combination thereof.

25. (Previously Presented) The method of claim 13, wherein said dosage form comprises paroxetine or a pharmaceutically acceptable salt thereof in a crystalline form.

26. (Previously Presented) The method of claim 13, wherein said dosage form comprises paroxetine or a pharmaceutically acceptable salt thereof in an amorphous form.

Atty. Dkt. No. 091856-0158

### REMARKS

Applicant respectfully requests reconsideration of the application in view of the foregoing amendments and the following remarks.

Claim 13 is amended without prejudice or disclaimer to use the transitional phrase “consisting of”. No new matter is introduced. Upon entry of this amendment, claims 13-26 will remain pending. These claims are presented for reconsideration.

Claims 13-26 were rejected under the doctrine of obviousness-type double patenting for alleged obviousness over claims of U.S. 8,658,663 and U.S. 8,859,576. Claims 19 and 21 were rejected under the doctrine of obviousness-type double patenting for alleged obviousness over claims of U.S. 8,946,251. Without acquiescing to the merits of these rejections, Applicant submits herewith a Terminal Disclaimer that obviates these issues.

Claims 13-18, 20, and 22-26 were rejected under 35 USC § 101 for alleged same-invention type double patenting in view of claims 1-12 of U.S. 8,946,251. Without acquiescing to the merits of these rejections, Applicant believes that the foregoing amendments to independent claim 13 obviates these issues.

Applicant therefore believes that the application is in condition for allowance, and an early notice to that effect is earnestly solicited.

Atty. Dkt. No. 091856-0158

Should there be any questions regarding this submission, or should any issue remain, the  
he Examiner is invited to contact the undersigned by telephone to advance prosecution.

Respectfully submitted,

Date Feb 24, 2016

By Courtenay C Brinckerhoff

FOLEY & LARDNER LLP  
Customer Number: 22428  
Telephone: (202) 295-4094  
Facsimile: (202) 672-5399

Courtenay C. Brinckerhoff  
Attorney for Applicant  
Registration No. 37,288

Electronic Patent Application Fee Transmittal				
<b>Application Number:</b>		14577227		
<b>Filing Date:</b>		19-Dec-2014		
<b>Title of Invention:</b>		METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE		
<b>First Named Inventor/Applicant Name:</b>		Patricia Allison Tewes Richards		
<b>Filer:</b>		Courtenay C. Brinckerhoff/Christine Arthur		
<b>Attorney Docket Number:</b>		091856-0158		
Filed as Large Entity				
<b>Filing Fees for Utility under 35 USC 111(a)</b>				
<b>Description</b>	<b>Fee Code</b>	<b>Quantity</b>	<b>Amount</b>	<b>Sub-Total in USD(\$)</b>
<b>Basic Filing:</b>				
<b>Pages:</b>				
<b>Claims:</b>				
<b>Miscellaneous-Filing:</b>				
<b>Petition:</b>				
<b>Patent-Appeals-and-Interference:</b>				
<b>Post-Allowance-and-Post-Issuance:</b>				
<b>Extension-of-Time:</b>				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension - 3 months with \$0 paid	1253	1	1400	1400
<b>Miscellaneous:</b>				
<b>Total in USD (\$)</b>				<b>1400</b>

**Electronic Acknowledgement Receipt**

<b>EFS ID:</b>	25004505
<b>Application Number:</b>	14577227
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	5836
<b>Title of Invention:</b>	METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE
<b>First Named Inventor/Applicant Name:</b>	Patricia Allison Tewes Richards
<b>Customer Number:</b>	22428
<b>Filer:</b>	Courtenay C. Brinckerhoff/Christine Arthur
<b>Filer Authorized By:</b>	Courtenay C. Brinckerhoff
<b>Attorney Docket Number:</b>	091856-0158
<b>Receipt Date:</b>	24-FEB-2016
<b>Filing Date:</b>	19-DEC-2014
<b>Time Stamp:</b>	11:31:12
<b>Application Type:</b>	Utility under 35 USC 111(a)

**Payment information:**

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	\$ 1400
RAM confirmation Number	11285
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

'237 FH -0208

**File Listing:**

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment/Req. Reconsideration-After Non-Final Reject	response.pdf	3204251	no	5
			daea8e3f11d02ded8a61925dac054b34aab 4c081		

**Warnings:****Information:**

2	Fee Worksheet (SB06)	fee-info.pdf	31297	no	2
			338ae2606200f308b9a7951329937fb6179 b22ec		

**Warnings:****Information:**

<b>Total Files Size (in bytes):</b>			3235548
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**New Applications Under 35 U.S.C. 111**

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**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



## UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
 United States Patent and Trademark Office  
 Address: COMMISSIONER FOR PATENTS  
 P.O. Box 1450  
 Alexandria, Virginia 22313-1450  
 www.uspto.gov

## NOTICE OF ALLOWANCE AND FEE(S) DUE

22428 7590 03/18/2016  
 Foley & Lardner LLP  
 3000 K STREET N.W.  
 SUITE 600  
 WASHINGTON, DC 20007-5109

EXAMINER

KANTAMNENI, SHOBHA

ART UNIT

PAPER NUMBER

1627

DATE MAILED: 03/18/2016

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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14/577,227

12/19/2014

Patricia Allison Tewes Richards

091856-0158

5836

TITLE OF INVENTION: METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$960	\$0	\$0	\$960	06/20/2016

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.**

**THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.**

**HOW TO REPLY TO THIS NOTICE:**

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

**IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.**

PART B - Fee(s) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail** **Mail Stop ISSUE FEE**  
**Commissioner for Patents**  
**P.O. Box 1450**  
**Alexandria, Virginia 22313-1450**  
**or Fax** **(571)-273-2885**

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22428 7590 03/18/2016  
**Foley & Lardner LLP**  
**3000 K STREET N.W.**  
**SUITE 600**  
**WASHINGTON, DC 20007-5109**

#### Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/577,227	12/19/2014	Patricia Allison Tewes Richards	091856-0158	5836

TITLE OF INVENTION: METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$960	\$0	\$0	\$960	06/20/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
KANTAMNENI, SHOBHA	1627	514-277000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

- (1) The names of up to 3 registered patent attorneys or agents OR, alternatively, 1 \_\_\_\_\_
- (2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2 \_\_\_\_\_
- 3 \_\_\_\_\_

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☐ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies \_\_\_\_\_

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number \_\_\_\_\_ (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
- ☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature \_\_\_\_\_

Date \_\_\_\_\_

Typed or printed name \_\_\_\_\_

Registration No. \_\_\_\_\_



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/577,227	12/19/2014	Patricia Allison Tewes Richards	091856-0158	5836
22428	7590	03/18/2016	EXAMINER	
Foley & Lardner LLP 3000 K STREET N.W. SUITE 600 WASHINGTON, DC 20007-5109			KANTAMNENI, SHOBHA	
			ART UNIT	PAPER NUMBER
			1627	

DATE MAILED: 03/18/2016

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**  
 (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

## OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

## Privacy Act Statement

**The Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

<b>Notice of Allowability</b>	<b>Application No.</b> 14/577,227	<b>Applicant(s)</b> RICHARDS, PATRICIA ALLISON TEWES	
	<b>Examiner</b> SHOBHA KANTAMNENI	<b>Art Unit</b> 1627	<b>AIA (First Inventor to File) Status</b> No

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--**

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 02/24/2016.  
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on \_\_\_\_.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on \_\_\_\_; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are 13-26. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see [http://www.uspto.gov/patents/init\\_events/pph/index.jsp](http://www.uspto.gov/patents/init_events/pph/index.jsp) or send an inquiry to [PPHfeedback@uspto.gov](mailto:PPHfeedback@uspto.gov).
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

- a) ☐ All    b) ☐ Some    \*c) ☐ None of the:
  1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\* Certified copies not received: \_\_\_\_.

Applicant has **THREE MONTHS FROM THE "MAILING DATE"** of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in **ABANDONMENT** of this application.  
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5. ☐ **CORRECTED DRAWINGS** ( as "replacement sheets") must be submitted.  
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date \_\_\_\_.  
**Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**
6. ☐ **DEPOSIT OF and/or INFORMATION** about the deposit of **BIOLOGICAL MATERIAL** must be submitted. Note the attached Examiner's comment regarding **REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL**.

**Attachment(s)**

<ol style="list-style-type: none"> <li>1. <input type="checkbox"/> Notice of References Cited (PTO-892)</li> <li>2. <input type="checkbox"/> Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date ____</li> <li>3. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit of Biological Material</li> <li>4. <input type="checkbox"/> Interview Summary (PTO-413), Paper No./Mail Date ____</li> </ol>	<ol style="list-style-type: none"> <li>5. <input type="checkbox"/> Examiner's Amendment/Comment</li> <li>6. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance</li> <li>7. <input type="checkbox"/> Other ____</li> </ol>
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Application/Control Number: 14/577,227  
Art Unit: 1627

Page 2

The present application is being examined under the pre-AIA first to invent provisions.

## **DETAILED ACTION**

### **EXAMINER'S STATEMENT OF REASONS FOR ALLOWANCE**

The following is an examiner's statement of reasons for allowance:

1) The rejection of claims 13-26 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of US patent No. 8,658,663, in view of Gould (International Journal of Pharmaceutics, 33 1986, pages 201-217, PTO-892 of record in the '663) is herein withdrawn. Note: Applicant has filed Terminal Disclaimer.

2) The rejection of claims 13-26 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of US patent No. 8,859,576, in view of Gould (International Journal of Pharmaceutics, 33 1986, pages 201-217, PTO-892 of record in the '663) is herein withdrawn. Note: Applicant has filed Terminal Disclaimer.

3) The rejection of claims 19, 21 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of US Patent No. 8,946,251, in view of Gould (International Journal of Pharmaceutics, 33 1986, pages 201-217, PTO-892 of record in the '663) is herein withdrawn. Note: Applicant has filed Terminal Disclaimer.

Application/Control Number: 14/577,227

Page 3

Art Unit: 1627

4) Applicant's amendment overcomes the rejection of claims 13-18, 20, 22-26 under 35 U.S.C. 101 as claiming the same invention as that of claims 1-12 of prior U.S. Patent No. 8,946,251.

In light of the Applicant's arguments and amendment filed on 02/24/2015, claims 13-26 are allowed and renumbered to claims 1-14.

The instant invention as defined by claims 13-26 is novel, and allowable over prior art.

#### *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni, Ph.D whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 8am-4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Application/Control Number: 14/577,227

Page 4

Art Unit: 1627

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHOBHA KANTAMNENI/  
Primary Examiner, Art Unit 1627



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## BIB DATA SHEET

CONFIRMATION NO. 5836

<b>SERIAL NUMBER</b> 14/577,227	<b>FILING or 371(c) DATE</b> 12/19/2014 <b>RULE</b>	<b>CLASS</b> 514	<b>GROUP ART UNIT</b> 1627	<b>ATTORNEY DOCKET NO.</b> 091856-0158	
<b>APPLICANTS</b> NOVEN THERAPEUTICS, LLC, Miami, FL; <b>INVENTORS</b> Patricia Allison Tewes Richards, Scarsdale, NY; <b>** CONTINUING DATA *****</b> This application is a CON of 14/157,992 01/17/2014 PAT 8946251 which is a CON of 12/292,960 12/01/2008 PAT 8658663 which is a CON of 11/499,586 08/04/2006 ABN <b>** FOREIGN APPLICATIONS *****</b> <b>** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **</b> 01/08/2015					
Foreign Priority claimed <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No 35 USC 119(a-d) conditions met <input type="checkbox"/> Yes <input type="checkbox"/> No Verified and /SHOBHA KANTAMNENI/ Acknowledged Examiner's Signature	<input type="checkbox"/> Met after Allowance sk Initials	<b>STATE OR COUNTRY</b> NY	<b>SHEETS DRAWINGS</b> 0	<b>TOTAL CLAIMS</b> 14	<b>INDEPENDENT CLAIMS</b> 1
<b>ADDRESS</b> Foley & Lardner LLP 3000 K STREET N.W. SUITE 600 WASHINGTON, DC 20007-5109 UNITED STATES					
<b>TITLE</b> METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE					
<b>FILING FEE RECEIVED</b> 1740	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:		<input type="checkbox"/> All Fees <input type="checkbox"/> 1.16 Fees (Filing) <input type="checkbox"/> 1.17 Fees (Processing Ext. of time) <input type="checkbox"/> 1.18 Fees (Issue) <input type="checkbox"/> Other _____ <input type="checkbox"/> Credit		

<b>Search Notes</b>  	<b>Application/Control No.</b>  14577227	<b>Applicant(s)/Patent Under Reexamination</b>  RICHARDS, PATRICIA ALLISON TEWES
	<b>Examiner</b>  SHOBHA KANTAMNENI	<b>Art Unit</b>  1627

CPC- SEARCHED		
Symbol	Date	Examiner
A61K 31/4525	3/4/2016	ks

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor, Assignee search updated on PALM	3/4/2016	ks
EAST, NPL search done	3/4/2016	ks


INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
C07D 317/03		3/4/2016	ks
C07D 211/22		3/4/2016	ks
A61K 31/4525		3/4/2016	ks

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[illegible]


CPC Combination Sets				
Symbol	Type	Set	Ranking	Version

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	14	
/SHOBHA KANTAMNENI/ Primary Examiner.Art Unit 1627	03/04/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

<b>Issue Classification</b> 	<b>Application/Control No.</b> 14577227	<b>Applicant(s)/Patent Under Reexamination</b> RICHARDS, PATRICIA ALLISON TEWES
	<b>Examiner</b> SHOBHA KANTAMNENI	<b>Art Unit</b> 1627

US ORIGINAL CLASSIFICATION						INTERNATIONAL CLASSIFICATION												
CLASS			SUBCLASS			CLAIMED					NON-CLAIMED							
514			277			A	6	1	K	31 / 435 (2006.01.01)								
CROSS REFERENCE(S)																		
CLASS		SUBCLASS (ONE SUBCLASS PER BLOCK)																
514	183	463																

NONE		<b>Total Claims Allowed:</b>	
		14	
(Assistant Examiner)	(Date)		
/SHOBHA KANTAMNENI/ Primary Examiner.Art Unit 1627	03/04/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

<b>Issue Classification</b> 	<b>Application/Control No.</b> 14577227	<b>Applicant(s)/Patent Under Reexamination</b> RICHARDS, PATRICIA ALLISON TEWES
	<b>Examiner</b> SHOBHA KANTAMNENI	<b>Art Unit</b> 1627

<input type="checkbox"/> Claims renumbered in the same order as presented by applicant								<input type="checkbox"/> CPA		<input checked="" type="checkbox"/> T.D.		<input type="checkbox"/> R.1.47			
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	13														
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14	26														

NONE		<b>Total Claims Allowed:</b>	
		14	
(Assistant Examiner)	(Date)	O.G. Print Claim(s)	O.G. Print Figure
/SHOBHA KANTAMNENI/ Primary Examiner.Art Unit 1627	03/04/2016	1	NONE
(Primary Examiner)	(Date)		

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**Courtesy Reminder for  
Application Serial No: 14/577,227**

Attorney Docket No: 091856-0158

Customer Number: 22428

Date of Electronic Notification: 03/18/2016

This is a courtesy reminder that new correspondence is available for this application. If you have not done so already, please review the correspondence. The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

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ipdocketing@foley.com

To view your correspondence online or update your email addresses, please visit us anytime at <https://sportal.uspto.gov/secure/myportal/privatepair>. If you have any questions, please email the Electronic Business Center (EBC) at [EBC@uspto.gov](mailto:EBC@uspto.gov) or call 1-866-217-9197.

## PART B - FEE(S) TRANSMITTAL

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(Depositor's name)
(Signature)
(Date)

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TITLE OF INVENTION: METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE

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KANTAMNENI, SHOBHA	1627	514-277000

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2. For printing on the patent front page, list

- (1) The names of up to 3 registered patent attorneys or agents OR, alternatively,  
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FOLEY & LARDNER LLP

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

NOVEN THERAPEUTICS, LLC

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Miami, Florida

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☒ Issue Fee  
☐ Publication Fee (No small entity discount permitted)  
☐ Advance Order - # of Copies \_\_\_\_\_

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.  
☒ Payment by credit card. Form PTO-2038 is attached.  
☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 19-0741 (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29  
☐ Applicant asserting small entity status. See 37 CFR 1.27  
☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature

Courtenay C. Brinckerhoff

Typed or printed name

Date

June 17, 2016

Registration No.

37,288

Electronic Patent Application Fee Transmittal				
<b>Application Number:</b>		14577227		
<b>Filing Date:</b>		19-Dec-2014		
<b>Title of Invention:</b>		METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE		
<b>First Named Inventor/Applicant Name:</b>		Patricia Allison Tewes Richards		
<b>Filer:</b>		Courtenay C. Brinckerhoff		
<b>Attorney Docket Number:</b>		091856-0158		
Filed as Large Entity				
<b>Filing Fees for Utility under 35 USC 111(a)</b>				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
<b>Basic Filing:</b>				
<b>Pages:</b>				
<b>Claims:</b>				
<b>Miscellaneous-Filing:</b>				
<b>Petition:</b>				
<b>Patent-Appeals-and-Interference:</b>				
<b>Post-Allowance-and-Post-Issuance:</b>				
Utility Appl Issue Fee	1501	1	960	960

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				960

**Electronic Acknowledgement Receipt**

<b>EFS ID:</b>	26095599
<b>Application Number:</b>	14577227
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	5836
<b>Title of Invention:</b>	METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE
<b>First Named Inventor/Applicant Name:</b>	Patricia Allison Tewes Richards
<b>Customer Number:</b>	22428
<b>Filer:</b>	Courtenay C. Brinckerhoff
<b>Filer Authorized By:</b>	
<b>Attorney Docket Number:</b>	091856-0158
<b>Receipt Date:</b>	17-JUN-2016
<b>Filing Date:</b>	19-DEC-2014
<b>Time Stamp:</b>	11:58:42
<b>Application Type:</b>	Utility under 35 USC 111(a)

**Payment information:**

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	\$960
RAM confirmation Number	9035
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

'237 FH -0227

**File Listing:**

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	issuefee.pdf	121880	no	1
			637ffa70efafc30f8a63a65d98c93bd730704d08		

**Warnings:****Information:**

2	Fee Worksheet (SB06)	fee-info.pdf	30933	no	2
			683f669e84810e3286abd5ee0a6af78f5f7606a0		

**Warnings:****Information:**

<b>Total Files Size (in bytes):</b>			152813
-------------------------------------	--	--	--------

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



## UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
**United States Patent and Trademark Office**  
 Address: COMMISSIONER FOR PATENTS  
 P.O. Box 1450  
 Alexandria, Virginia 22313-1450  
[www.uspto.gov](http://www.uspto.gov)

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/577,227	07/19/2016	9393237	091856-0158	5836

22428 7590 06/29/2016

Foley & Lardner LLP  
 3000 K STREET N.W.  
 SUITE 600  
 WASHINGTON, DC 20007-5109

**ISSUE NOTIFICATION**

The projected patent number and issue date are specified above.

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**  
 (application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

**APPLICANT(s)** (Please see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

Patricia Allison Tewes Richards, Scarsdale, NY;  
 NOVEN THERAPEUTICS, LLC, Miami, FL;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit [SelectUSA.gov](http://SelectUSA.gov).

**STATEMENT UNDER 37 CFR 3.73(c)**Applicant/Patent Owner: SEBELA INTERNATIONAL LIMITEDApplication No./Patent No.: 14/577,227Filed/Issue Date: December 19, 2014Titled: METHOD OF TREATING THERMOREGULATORY DISFUNCTION WITH PAROXETINESEBELA INTERNATIONAL LIMITED, a CORPORATION

(Name of Assignee)

(Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose one of options 1, 2, 3 or 4 below):

1. ☒ The assignee of the entire right, title, and interest.
2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):
- ☐ The extent (by percentage) of its ownership interest is \_\_\_\_%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.
- ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (e.g., bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose one of options A or B below):

- A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel \_\_\_\_\_, Frame \_\_\_\_\_, or for which a copy thereof is attached.
- B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: RICHARDS, PATRICIA ALLISON TEWES To: JDS PHARMACEUTICALS, LLCThe document was recorded in the United States Patent and Trademark Office at  
Reel 018388, Frame 0706, or for which a copy thereof is attached.2. From: JDS PHARMACEUTICALS, LLC To: NOVEN THERAPEUTICS, LLCThe document was recorded in the United States Patent and Trademark Office at  
Reel 020565, Frame 0921, or for which a copy thereof is attached.

[Page 1 of 2]

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

'237 FH -0230

**STATEMENT UNDER 37 CFR 3.73(c)**3. From: NOVEN THERAPEUTICS, LLC To: SEBELA INTERNATIONAL LIMITEDThe document was recorded in the United States Patent and Trademark Office at  
Reel 039334, Frame 0114, or for which a copy thereof is attached.

4. From: \_\_\_\_\_ To: \_\_\_\_\_

The document was recorded in the United States Patent and Trademark Office at  
Reel \_\_\_\_\_, Frame \_\_\_\_\_, or for which a copy thereof is attached.

5. From: \_\_\_\_\_ To: \_\_\_\_\_

The document was recorded in the United States Patent and Trademark Office at  
Reel \_\_\_\_\_, Frame \_\_\_\_\_, or for which a copy thereof is attached.

6. From: \_\_\_\_\_ To: \_\_\_\_\_

The document was recorded in the United States Patent and Trademark Office at  
Reel \_\_\_\_\_, Frame \_\_\_\_\_, or for which a copy thereof is attached.☐ Additional documents in the chain of title are listed on a supplemental sheet(s).☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Sean Myers-Payne  
Signature11/8/16  
DateSean Myers-Payne42,920

Printed or Typed Name

Title or Registration Number

## Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO**

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:



Practitioners associated with Customer Number:

07055

**OR**

Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number

Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignments documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:



The address associated with Customer Number:

07055

**OR**

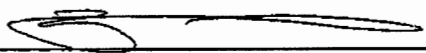
<input type="checkbox"/>	Firm or Individual Name			
<input type="checkbox"/>	Address			
	City	State	Zip	
	Country			
	Telephone	Email		

Assignee Name and Address: SEBELA INTERNATIONAL LIMITED  
H.P. HOUSE, 21 LAFFAN STREET  
HAMILTON, BERMUDA HM09

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of The practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

**SIGNATURE of Assignee of Record**

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date	
Name	ZOE HANSON	Telephone	
Title	DIRECTOR		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

**Electronic Acknowledgement Receipt**

<b>EFS ID:</b>	27457563
<b>Application Number:</b>	14577227
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	5836
<b>Title of Invention:</b>	METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE
<b>First Named Inventor/Applicant Name:</b>	Patricia Allison Tewes Richards
<b>Customer Number:</b>	22428
<b>Filer:</b>	Sean Christopher Myers-Payne/Manon Lozach
<b>Filer Authorized By:</b>	Sean Christopher Myers-Payne
<b>Attorney Docket Number:</b>	091856-0158
<b>Receipt Date:</b>	10-NOV-2016
<b>Filing Date:</b>	19-DEC-2014
<b>Time Stamp:</b>	11:41:22
<b>Application Type:</b>	Utility under 35 USC 111(a)

**Payment information:**

Submitted with Payment	no
------------------------	----

**File Listing:**

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		P51150_SADS_373_Statement _And_POA.pdf	515142 8e70242a8b321fe9c5b75f1ae9a91cd4f0acca ffa	yes	11

Multipart Description/PDF files in .zip description

Case 2:17-cv-04964-CCC-MF Document 22 Filed 07/20/17 Page 240 of 500 PageID: 1917

	Multipart Description/PDF files in .zip description		
	Document Description	Start	End
	Application Data Sheet	1	7
	Power of Attorney	8	11
Warnings:			
Information:			
Total Files Size (in bytes):		515142	
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><b><u>New Applications Under 35 U.S.C. 111</u></b> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><b><u>National Stage of an International Application under 35 U.S.C. 371</u></b> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><b><u>New International Application Filed with the USPTO as a Receiving Office</u></b> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>			

P51150

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s) : Patricia Allison Tewes RICHARDS      Conf. No : 5836  
Appl. No. : 14/577,227      Examiner : KANTAMNENI, SHOBHA  
Filed : December 19, 2014      Group Art Unit : 1627  
For : METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH  
PAROXETINE

**COVER LETTER REGARDING SUBMISSION OF  
APPLICATION DATA SHEET UNDER 37 C.F.R. 1.76(c)(2)**

Commissioner for Patents  
U.S. Patent and Trademark Office  
Customer Service Window, Mail Stop \_\_\_\_\_  
Randolph Building  
401 Dulany Street  
Alexandria, VA 22314

Sir:

In accordance with 37 C.F.R. 1.76(c)(2), Applicant(s) submit(s) for the above-captioned application having a U.S. filing date after September 16, 2012, an Application Data Sheet (ADS) with information provided only in the section to be revised. In particular, the information being revised is in the following section(s):

- ☐ Application Information
- ☐ Inventor Information
- ☒ Correspondence Information
- ☒ Representative Information
- ☐ Domestic Benefit/National Stage Information
- ☐ Foreign Priority Information
- ☐ Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications
- ☒ Applicant Information
- ☒ Non-Applicant Assignee Information

Accordingly, Applicant(s) request(s) entry of the information provided in the attached

Application Data Sheet.

{P51150 02911087.DOC}

'237 FH -0236

P51150

Furthermore, the Applicant respectfully requests that the United States Patent and Trademark Office issue a corrected Official Filing Receipt in the above-identified application.

Should there be any questions with regard to this submission, the Examiner is requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,  
Patricia Allison Tewes RICHARDS

A handwritten signature in black ink, appearing to read "Sean Myers-Payne". The signature is fluid and cursive, with a horizontal line drawn underneath it.

Sean Myers-Payne  
Reg. No. 42920

November 3, 2016  
GREENBLUM & BERNSTEIN, P.L.C.  
1950 Roland Clarke Place  
Reston, VA 20191  
(703) 716-1191

P51150

**Application Data Sheet****Application Information**

Application Number:: 14/577,227  
 Filing Date:: December 19, 2014  
 Application Type::  
 Subject Matter::  
 Suggested Classification::  
 Suggested Group Art Unit::  
 CD-ROM or CD-R?:  
 Number of CD disks::  
 Number of copies of CDs::  
 Sequence submission?:  
 Computer Readable Form (CRF)?:  
 Number of copies of CRF::  
 Title:: METHOD OF TREATING  
 THERMOREGULATORY DYSFUNCTION  
 WITH PAROXETINE  
 Attorney Docket Number:: ~~091856-0158~~ **P51150**  
 Request for Early Publication?:  
 Request for Non-Publication?:  
 Suggested Drawing Figure:  
 Total Drawing Sheets::  
 Small Entity?:  
 Latin name::  
 Variety denomination name::  
 Petition included?:  
 Petition Type::  
 Licensed US Govt. Agency::  
 Contract or Grant Numbers::  
 Secrecy Order in Parent Appl.?:

P51150

## **Inventor Information**

Inventor 1::

Given Name::

Middle Name::

Family Name::

Name Suffix::

City of Residence::

State or Province of Residence::

Country of Residence::

Street of mailing address::

City of mailing address::

State or Province of mailing address::

Country of mailing address::

Postal or Zip Code of mailing address::

## **Correspondence Information**

Correspondence Customer Number::

22428 07055

Name::

Foley & Lardner LLP

**GREENBLUM & BERNSTEIN P.L.C.**

Street of mailing address::

~~3000 K STREET N.W.~~

~~SUITE 600~~

**1950 Roland Clarke Place**

City of mailing address::

~~WASHINGTON DC~~

**Reston**

State of Province of mailing address::

**VA**

Country of mailing address::

**USA**

Postal or Zip Code of mailing address::

20007-5109

**20191**

Phone number::

**(703) 716-1191**

Fax Number::

**(703) 716-1180**

E-Mail address::

**gbpatent@gbpatent.com**

{P51150 02911087.DOC}

P51150

**Representative Information**

Representative Customer Number:	<del>22428</del> <u>07055</u>
---------------------------------	-------------------------------

**-OR-**

Representative Designation::	Registration Number::	Representative Name::

**Domestic Benefit/National Stage Information:**

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Prior Application Status			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)

**Foreign Priority Information:**

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country	Parent Filing Date (YYYY-MM-DD)	Access code:: (if applicable)

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File)  
Transition Applications**

<input type="checkbox"/>	This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
--------------------------	--

P51150

**Applicant Information**

Applicant 1:: ☒ Assignee ☐ Legal Representative under 35 U.S.C 117  
☐ Joint Inventor ☐ Person to whom the inventor is obligated to assign  
☐ Person who shows sufficient proprietary interest

If applicant is the legal representative, the inventor is:: ☐ Deceased ☐ Legally incapacitated

Given Name:: Patricia

Middle Name:: Allison Tewes

Family Name:: RICHARDS

Name Suffix::

Applicant is an Organization:: Yes

Applicant Name:: SEBELA INTERNATIONAL LIMITED

Mailing address:: ~~3212 Bay Drive~~ H.P. House, 21 Laffan Street

City of mailing address:: ~~Bradenton~~ Hamilton

State or Province of mailing address:: Florida

Country of mailing address:: ~~United States~~ Bermuda

Postal or Zip Code of mailing address:: 34207 HM09

**Assignee Information Including Non-Applicant Assignee Information:**

Assignee 1:: ☒ Assignee is an Organization

Given Name::

Middle Name::

Family Name::

Name Suffix::

Applicant is an Organization::

Assignee Name:: NOVEN THERAPEUTICS, LLC

SEBELA INTERNATIONAL LIMITED

Mailing address:: ~~11960 SW 144TH STREET~~

H.P. HOUSE, 21 LAFFAN STREET

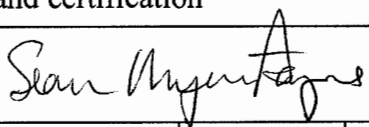
City of mailing address:: ~~MIAMI~~

HAMILTON

{P51150 02911087.DOC}

P51150

State or Province of mailing address:: FLORIDACountry of mailing address:: BERMUDAPostal or Zip Code of mailing address: 33186HM09**Signature:**

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certification					
Signature				Date (YYYY-MM-DD)	2016-11-09
First Name	Sean	Last Name	Myers-Payne	Registration Number	42,920



## UNITED STATES PATENT AND TRADEMARK OFFICE

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 Alexandria, Virginia 22313-1450  
 www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/577,227	12/19/2014	Patricia Allison Tewes Richards	091856-0158

7055  
 GREENBLUM & BERNSTEIN, P.L.C.  
 1950 ROLAND CLARKE PLACE  
 RESTON, VA 20191

**CONFIRMATION NO. 5836**  
**POA ACCEPTANCE LETTER**



Date Mailed: 11/21/2016

### NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/10/2016.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/mabebe/



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14/577,227	12/19/2014	Patricia Allison Tewes Richards	091856-0158

22428  
 Foley & Lardner LLP  
 3000 K STREET N.W.  
 SUITE 600  
 WASHINGTON, DC 20007-5109

**CONFIRMATION NO. 5836**  
**POWER OF ATTORNEY NOTICE**



Date Mailed: 11/21/2016

### NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/10/2016.

- The Power of Attorney to you in this application has been revoked by the applicant. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
14/577,227	12/19/2014	1627	1740	P51150	14	1

CONFIRMATION NO. 5836

CORRECTED FILING RECEIPT

7055

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 1950 ROLAND CLARKE PLACE  
 RESTON, VA 20191



CC000000087288623

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**Inventor(s)**

Patricia Allison Tewes Richards, Scarsdale, NY;

**Applicant(s)**

NOVEN THERAPEUTICS, LLC, Miami, FL;  
 SEBELA INTERNATIONAL LIMITED, Hamilton, BERMUDA;

**Assignment For Published Patent Application**

SEBELA INTERNATIONAL LIMITEDH, HAMILTON, BERMUDA

**Power of Attorney:** The patent practitioners associated with Customer Number 7055**Domestic Priority data as claimed by applicant**

This application is a CON of 14/157,992 01/17/2014 PAT 8946251  
 which is a CON of 12/292,960 12/01/2008 PAT 8658663  
 which is a CON of 11/499,586 08/04/2006 ABN

**Foreign Applications** for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

*Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.*

**Permission to Access Application via Priority Document Exchange:** Yes**Permission to Access Search Results:** No

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

**If Required, Foreign Filing License Granted:** 01/08/2015

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/577,227**

**Projected Publication Date:** Not Applicable

**Non-Publication Request:** No

**Early Publication Request:** No

**Title**

METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE

**Preliminary Class**

514

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

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### **Title 35, United States Code, Section 184**

### **Title 37, Code of Federal Regulations, 5.11 & 5.15**

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The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

#### **NOT GRANTED**

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---

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The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit <http://www.SelectUSA.gov> or call +1-202-482-6800.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s) :Patricia Allison Tewes RICHARDS Group Art Unit : 1627  
Appl. No. : 14/577,227 Examiner : KANTAMNENI, SHOBHA  
Filed : December 19, 2014 Confirmation No. : 5836  
For : METHOD OF TREATING THERMOREGULATORY DISFUNCTION WITH  
PAROXETINE

**REQUEST FOR CORRECTION OF FILING RECEIPT**

Commissioner for Patents  
U.S. Patent and Trademark Office  
Randolph Building  
401 Dulany Street  
Alexandria, VA 22314

Madam:

The name of the Applicant as claimed by applicant of the above-identified application, as it appears on the Official Filing Receipt, is incorrect. Attached please find a copy of the Official Filing Receipt with the requested change noted thereon. Please list the name of the Applicant as claimed by applicant as follows:

**SEBELA INTERNATIONAL LIMITED, Hamilton, BERMUDA**

instead of :

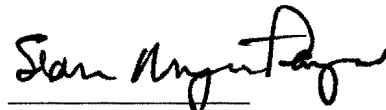
**NOVEN THERAPEUTICS, LLC, Miami, FL**

**SEBELA INTERNATIONAL LIMITED, Hamilton, BERMUDA**

and forward a corrected copy of the filing Receipt to the undersigned.

The U.S. Patent and Trademark Office is hereby authorized to credit any overpayment or charge any additional fee to the Deposit Account No. 19-0089.

Respectfully Submitted,  
Patricia Allison Tewes RICHARDS



Sean Myers-Payne  
Reg. No. 42920

December 6, 2016  
GREENBLUM & BERNSTEIN, P.L.C.  
1950 Roland Clarke Place  
Reston, VA 20191  
(703) 716-1191



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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
14/577,227	12/19/2014	1627	1740	P51150	14	1

7055  
 GREENBLUM & BERNSTEIN, P.L.C.  
 1950 ROLAND CLARKE PLACE  
 RESTON, VA 20191

**CONFIRMATION NO. 5836**  
**CORRECTED FILING RECEIPT**



CC000000087268623

Date Mailed: 11/21/2016

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

**Inventor(s)**

Patricia Allison Tewes Richards, Scarsdale, NY;

SEBELA INTERNATIONAL LIMITED, Hamilton, BERMUDA

**Applicant(s)**

NOVEN THERAPEUTICS, LLC, Miami, FL;  
 SEBELA INTERNATIONAL LIMITED, Hamilton, BERMUDA;

**Assignment For Published Patent Application**

SEBELA INTERNATIONAL LIMITEDH, HAMILTON, BERMUDA

**Power of Attorney:** The patent practitioners associated with Customer Number 7055**Domestic Priority data as claimed by applicant**

This application is a CON of 14/157,992 01/17/2014 PAT 8946251  
 which is a CON of 12/292,960 12/01/2008 PAT 8658663  
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**Permission to Access Application via Priority Document Exchange:** Yes**Permission to Access Search Results:** No

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

**If Required, Foreign Filing License Granted:** 01/08/2015

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/577,227**

**Projected Publication Date:** Not Applicable

**Non-Publication Request:** No

**Early Publication Request:** No  
**Title**

METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE

**Preliminary Class**

514

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

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CONFIRMATION NO. 5836

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CC000000067266623

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**Projected Publication Date:** Not Applicable

**Non-Publication Request:** No

**Early Publication Request:** No  
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**Preliminary Class**

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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**Title 35, United States Code, Section 184**  
**Title 37, Code of Federal Regulations, 5.11 & 5.15**

**GRANTED**

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

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**NOT GRANTED**

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit <http://www.SelectUSA.gov> or call +1-202-482-6800.

**Electronic Acknowledgement Receipt**

<b>EFS ID:</b>	27720602
<b>Application Number:</b>	14577227
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	5836
<b>Title of Invention:</b>	METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE
<b>First Named Inventor/Applicant Name:</b>	Patricia Allison Tewes Richards
<b>Customer Number:</b>	7055
<b>Filer:</b>	Sean Christopher Myers-Payne/Manon Lozach
<b>Filer Authorized By:</b>	Sean Christopher Myers-Payne
<b>Attorney Docket Number:</b>	P51150
<b>Receipt Date:</b>	07-DEC-2016
<b>Filing Date:</b>	19-DEC-2014
<b>Time Stamp:</b>	14:08:35
<b>Application Type:</b>	Utility under 35 USC 111(a)

**Payment information:**

Submitted with Payment	no
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**File Listing:**

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Corrected Filing Receipt	P51150_Request_For_Corrected_OFR.pdf	454803 83ed851004a51276549b12c015ba88039ec c6000	no	7

**Warnings:****'237 FH -0255**

**Information:****Total Files Size (in bytes):**

454803

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

# EXHIBIT 35



## DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

ANDA 207139

## ANDA APPROVAL

Actavis Laboratories FL, Inc.  
2945 West Corporate Lakes Blvd., Suite B  
Weston, FL 33331  
Attention: Janet Vaughn  
Senior Director, Regulatory Affairs

Dear Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on April 10, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Paroxetine Capsules, 7.5 mg.

Reference is also made to the complete response letter issued by this office on November 30, 2015, and to your amendments received on June 10, June 28, and November 23, 2016; and February 8, February 17, and May 22, 2017.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is **approved**, effective on the date of this letter. The Office of Bioequivalence has determined your Paroxetine Capsules, 7.5 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Brisdelle Capsules, 7.5 mg, of Sebela Ireland Ltd. (Sebela). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

The RLD upon which you have based your ANDA, Sebela's Brisdelle Capsules, 7.5 mg, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
7,598,271 (the '271 patent)	May 4, 2025
8,658,663 (the '663 patent)	April 6, 2029
8,946,251 (the '251 patent)	August 4, 2026
9,393,237 (the '237 patent)	August 4, 2026

ANDA 207139  
Page 2

Your ANDA contains paragraph IV certifications to each of the patents<sup>1</sup> under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Paroxetine Capsules, 7.5 mg, under this ANDA. You have notified the Agency that Actavis Laboratories FL, Inc. (Actavis) complied with the requirements of section 505(j)(2)(B) of the FD&C Act and that litigation was initiated within the statutory 45-day period against Actavis for infringement of the '271, '663, and '251 patents in the United States District Court for the District of New Jersey [Noven Therapeutics, LLC v. Actavis Laboratories FL, Inc., Actavis Pharma, Inc., Andrx Corp., and Actavis, Inc., Civil Action Nos. 2:14-cv-06414 and 15-cv-06225]. Although this litigation remains ongoing, the 30-month period identified in section 505(j)(5)(B)(iii) of the FD&C Act, during which FDA was precluded from approving your ANDA, has expired.

Under section 506A of FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

### **REPORTING REQUIREMENTS**

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

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<sup>1</sup> The Agency notes that the '251 and '237 patents were submitted to the Agency after submission of your ANDA. Litigation, if any, with respect to these patents would not create a statutory stay of approval.

ANDA 207139  
Page 3

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **ANNUAL FACILITY FEES**

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at

<http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. The SPL will be accessible via publicly available labeling repositories.

ANDA 207139  
Page 4

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: [www.fda.gov/ectd](http://www.fda.gov/ectd).

Sincerely yours,

*{See appended electronic signature page}*

For Priya Shah, PharmD  
Acting Deputy Director  
Office of Regulatory Operations  
Office of Generic Drugs  
Center for Drug Evaluation and Research



Heidi  
Lee

Digitally signed by Heidi Lee  
Date: 6/20/2017 12:47:47PM  
GUID: 52795fe90009070673e7de063d080d1f

# EXHIBIT 36

**From:** [Askuvich, Alissa](#)  
**To:** [FIRM-Noven-Brisdelle@foley.com](mailto:FIRM-Noven-Brisdelle@foley.com)  
**Cc:** [Actavis-Brisdelle Team](#)  
**Subject:** In re Sebela Patent Litigation - Actavis Production  
**Date:** Thursday, June 22, 2017 11:31:17 AM  
**Attachments:** [2017 06 22 Production.zip](#)

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Counsel:

Attached please find Actavis Laboratories' s production documents bearing production numbers ACTBRIS0102318 - ACTBRIS0102322. The attached documents contain confidential information of Actavis and therefore are being produced pursuant to the Discovery Confidentiality Order (Dkt. 69) in Civil Action No. 14-cv-06414-CCC-JBC.

Best Regards,  
Alissa

**Alissa Askuvich**

Paralegal  
312.379.7610 | Direct  
[aaskuvich@brinksgilson.com](mailto:aaskuvich@brinksgilson.com)



**BRINKS GILSON & LIONE**

NBC Tower - Suite 3600 | 455 N. Cityfront Plaza Drive | Chicago, IL 60611

**Please Note:** This message is intended for the individual or entity named above and may constitute a privileged and confidential communication. If you are not the intended recipient, please do not read, copy, use, or disclose this message. Please notify the sender by replying to this message, and then delete the message from your system. Thank you.

# EXHIBIT 37

Anne B. Sekel  
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Phone: (212) 682-7474  
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asekel@foley.com

*Attorneys for Plaintiff  
Sebela International Limited*

**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

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SEBELA INTERNATIONAL LIMITED,

Plaintiff,

v.

ACTAVIS LABORATORIES FL, INC.,  
ACTAVIS PHARMA, INC., ANDRX CORP.,  
and ACTAVIS, INC.,

Defendants.

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Civil Action No. 2:14-cv-06414 (CCC-JBC)

Consolidated with 2:15-cv-06225 (CCC-JBC)

---

SEBELA INTERNATIONAL LIMITED,

Plaintiff,

v.

PRINCETON PHARMACEUTICAL INC.,  
SOLCO HEALTHCARE U.S., LLC, AND  
HUAHAI US INC.,

Defendants.

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Civil Action No. 2:14-cv-07400 (CCC-JBC)

Consolidated with 2:15-cv-05308 (CCC-JBC)

**JOINT STIPULATION**

Plaintiff Sebela International Limited (“Sebela” or “Plaintiff”), Defendants Princeton

Pharmaceutical Inc., Solco Healthcare U.S. LLC, and Huahai U.S. Inc. (collectively, “Princeton”)

and Actavis Laboratories FL, Inc., Actavis Pharma, Inc., Andrx Corp., and Actavis, Inc. (collectively, “Actavis,” and, together with Princeton, “Defendants”), appearing through their counsel state that:

WHEREAS Princeton filed Abbreviated New Drug Application No. 207188 with the Food and Drug Administration to obtain approval for its generic version of Brisdelle® (“Princeton ANDA Product”);

WHEREAS Actavis filed Abbreviated New Drug Application No. 207139 with the Food and Drug Administration to obtain approval for its generic version of Brisdelle® (“Actavis ANDA Product”);

WHEREAS Plaintiff has asserted that the filing of Princeton’s ANDA No. 207188 infringes Plaintiff’s U.S. Patent Nos. 5,874,447 (“’447 patent”); 7,598,271 (“’271 patent”); 8,658,663 (“’663 patent”); and 8,946,251 (“’251 patent”) (collectively “patents-in-suit”) under 35 U.S.C. § 271(e)(2), and that the manufacture, use, offer to sell, sale, and/or importation of the Princeton ANDA Product will infringe, *inter alia*, claims 1-6, 15-17, and 21-25 of the ’447 patent, claims 1-5 of the ’663 patent, and claims 1, 2, 4, 9, 10, 11, and 12 of the ’251 patent, under 35 U.S.C. §§ 271(a), (b), and (c);

WHEREAS Plaintiff has asserted that the filing of Actavis’s ANDA No. 207139 infringes Plaintiff’s U.S. Patent Nos. 5,874,447 (“’447 patent”); 7,598,271 (“’271 patent”); 8,658,663 (“’663 patent”); and 8,946,251 (“’251 patent”) (collectively, “patents-in-suit”) under 35 U.S.C. § 271(e)(2), and that the manufacture, use, offer to sell, sale, and/or importation of the Actavis ANDA Product will infringe, *inter alia*, claims 1-6, 15-17, and 21-25 of the ’447 patent, claims 1-5 of the ’663 patent, and claims 1, 2, 4, 9, 10, 11, and 12 of the ’251 patent, under 35 U.S.C. §§ 271(a), (b), and (c);

WHEREAS in the interest of streamlining issues for trial;

IT IS HEREBY STIPULATED that:

1. Plaintiff agrees to withdraw its asserted claims regarding the '447 patent in their entirety in exchange for Actavis's and Princeton's agreement not to launch their respective ANDA Products until at least June 10, 2017 (the expiration date of the '447 patent).

2. Plaintiff agrees to dismissal without prejudice of Count I (*i.e.*, ¶¶ 30-36) and Count II (*i.e.*, ¶¶ 37-42) of Plaintiff's Complaint (D.I. # 1 (14-cv-06414)) in exchange for Actavis's agreement to dismissal without prejudice of Actavis's First Counterclaim (*i.e.*, ¶¶ 9-14) and Second Counterclaim (*i.e.*, ¶¶ 15-20) of its Answer and Defenses to Complaint (D.I. # 5 (14-cv-06414)).

3. Plaintiff agrees to dismissal without prejudice of Count I (*i.e.*, ¶¶ 31-37) and Count II (*i.e.*, ¶¶ 38-43) of Plaintiff's Complaint (D.I. # 1 (14-cv-07400)) in exchange for Princeton's agreement to dismissal without prejudice of Count I (*i.e.*, ¶¶ 21-26) and Count II (*i.e.*, ¶¶ 27-30) of Princeton Pharmaceutical Inc.'s Answer, Defenses, and Counterclaims (D.I. # 8 (14-cv-07400)).

4. Princeton stipulates that making, offering to sell, selling, or importing the product that is the subject of ANDA No. 207188 according to its presently indicated use would actively induce and contribute to the infringement of claims 1, 2, and 5 of the '663 patent ("Asserted Claims of the '663 patent") and Princeton's submission of ANDA No. 207188 is an act of infringement of claims 1, 2, and 5 of the '663 patent pursuant to 35 U.S.C. § 271(e)(2)(A), provided that any such claim is not proven invalid.

5. Princeton stipulates that making, offering to sell, selling, or importing the product that is the subject of ANDA No. 207188 according to its presently indicated use would actively

induce and contribute to the infringement of claims 1, 2, 4, 9, and 10 of the '251 patent ("Asserted Claims of the '251 patent") and Princeton's submission of ANDA No. 207188 is an act of infringement of claims 1, 2, 4, 9, and 10 of the '251 patent pursuant to 35 U.S.C. § 271(e)(2)(A), provided that any such claim is not proven invalid.

6. Actavis stipulates that making, offering to sell, selling, or importing the product that is the subject of ANDA No. 207139 according to its presently indicated use would actively induce and contribute to the infringement of claims 1, 2, and 5 of the '663 patent ("Asserted Claims of the '663 patent") and Actavis's submission of ANDA No. 207139 is an act of infringement of claims 1, 2, and 5 of the '663 patent pursuant to 35 U.S.C. § 271(e)(2)(A), provided that any such claim is not proven invalid.

7. Actavis stipulates that making, offering to sell, selling, or importing the product that is the subject of ANDA No. 207139 according to its presently indicated use would actively induce and contribute to the infringement of claims 1, 2, 4, 9, and 10 of the '251 patent ("Asserted Claims of the '251 patent") and Actavis's submission of ANDA No. 207139 is an act of infringement of claims 1, 2, 4, 9, and 10 of the '251 patent pursuant to 35 U.S.C. § 271(e)(2)(A), provided that any such claim is not proven invalid.

8. Plaintiff agrees to withdraw asserted claims 3 and 4 the '663 patent. Plaintiff agrees that it does not, and will not, assert in this or any other action that claims 3 and 4 of the '663 patent are infringed by the manufacture, use, sale, offer to sell, and/or importation into the United States of the Princeton proposed product that is the subject matter of ANDA No. 207188 ("Princeton ANDA Product") or the manufacture, use, sale, offer to sell, and/or importation into the United States of the Actavis proposed product that is the subject matter of ANDA No. 207139 ("Actavis ANDA Product").

9. Plaintiff agrees to withdraw asserted claims 11 and 12 of the '251 patent.

Plaintiff agrees that it does not, and will not, assert in this or any other action that claims 11 and 12 of the '251 patent are infringed by the manufacture, use, sale, offer to sell, and/or importation into the United States of the Princeton ANDA Product or the manufacture, use, sale, offer to sell, and/or importation into the United States of the Actavis ANDA Product.

10. The parties' agreement and stipulations in paragraphs 4-9 resolves the parties' claim construction dispute with respect to the following claim terms:

Asserted Claim(s)	Claim Term
'663 patent, claim 3	"the paroxetine mesylate is in a crystalline form"
'663 patent, claim 4	"the paroxetine mesylate is in an amorphous form"
'251 patent, claim 11	"paroxetine or a pharmaceutically acceptable salt thereof in a crystalline form"
'251 patent, claim 12	"paroxetine or a pharmaceutically acceptable salt thereof in an amorphous form"

See Joint Claim Constr. Stmt., Dkt. No. 55-2, 55-3 (C.A. No. 2:14-cv-7400). The parties agree that the Court need not construe the claim terms listed above.

11. Except as expressly stated above, the parties maintain their respective claims and defenses regarding U.S. Patent Nos. 7,598,271; 8,658,663; and 8,946,251.

Dated: November 2, 2016

Respectfully submitted,

/s/Robert J. Fettweis

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**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

---

SEBELA INTERNATIONAL LIMITED,

Plaintiff,

v.

ACTAVIS LABORATORIES FL, INC.,  
ACTAVIS PHARMA, INC., ANDRX CORP.,  
and ACTAVIS, INC.,

Defendants.

Civil Action No. 2:14-cv-06414 (CCC-JBC)

Consolidated with 2:15-cv-06225 (CCC-JBC)

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SEBELA INTERNATIONAL LIMITED,

Plaintiff,

v.

PRINCETON PHARMACEUTICAL INC.,  
SOLCO HEALTHCARE U.S., LLC, AND  
HUAHAI US INC.,

Defendants.

Civil Action No. 2:14-cv-07400 (CCC-JBC)

Consolidated with 2:15-cv-05308 (CCC-JBC)

**[PROPOSED] ORDER REGARDING JOINT STIPULATION**

WHEREAS the Parties have entered into certain agreements in the interest of streamlining certain issues for trial, **IT IS SO ORDERED** that:

- Counts I and II of Sebela International Limited’s (“Sebela” or “Plaintiff”) Complaint (D.I. # 1 (14-cv-06414)) are hereby dismissed without prejudice;
- Actavis Laboratories FL, Inc., Actavis Pharma, Inc., Andrx Corp., and Actavis, Inc.’s (collectively, “Actavis”) First and Second Counterclaims of its Answer and Defenses to Complaint (D.I. # 5 (14-cv-06414)) are hereby dismissed without prejudice;

- Counts I and II of Sebela's Complaint (D.I. # 1 (14-cv-07400)) are hereby dismissed without prejudice;
- Counts I and II of Princeton Pharmaceutical Inc.'s Answer, Defenses, and Counterclaims (D.I. # 8 (14-cv-07400)) are hereby dismissed without prejudice;
- Princeton Pharmaceutical Inc., Solco Healthcare U.S. LLC, and Huahai U.S. Inc. (collectively, "Princeton") shall not (a) offer to sell or sell in the United States the products that are the subject of ANDA No. 207188 ("Princeton ANDA Product") prior to expiration of the '447 patent or (b) actively induce or assist any other person to offer to sell or sell in the United States the Princeton ANDA Product prior to the expiration of the '447 patent (thereby eliminating the need for trial of the parties' claims and counterclaims concerning the '447 patent);
- Actavis shall not (a) offer to sell or sell in the United States the products that are the subject of ANDA No. 207139 ("Actavis ANDA Product") prior to expiration of the '447 patent or (b) actively induce or assist any other person to offer to sell or sell in the United States the Actavis ANDA Product prior to the expiration of the '447 patent (thereby eliminating the need for trial of the parties' claims and counterclaims concerning the '447 patent);
- Princeton's making, offering to sell, selling, or importing the product that is the subject of ANDA No. 207188 according to its presently indicated use would actively induce and contribute to the infringement of claims 1, 2, and 5 of the '663 patent and Princeton's submission of ANDA No. 207188 is an act of infringement of claims 1, 2, and 5 of the '663 patent pursuant to 35 U.S.C. § 271(e)(2)(A), provided that any such claim is not proven invalid.

- Princeton's making, offering to sell, selling, or importing the product that is the subject of ANDA No. 207188 according to its presently indicated use would actively induce and contribute to the infringement of claims 1, 2, 4, 9, and 10 of the '251 patent and Princeton's submission of ANDA No. 207188 is an act of infringement of claims 1, 2, 4, 9, and 10 of the '251 patent pursuant to 35 U.S.C. § 271(e)(2)(A), provided that any such claim is not proven invalid.
- Actavis's making, offering to sell, selling, or importing the product that is the subject of ANDA No. 207139 according to its presently indicated use would actively induce and contribute to the infringement of claims 1, 2, and 5 of the '663 patent and Actavis's submission of ANDA No. 207139 is an act of infringement of claims 1, 2, and 5 of the '663 patent pursuant to 35 U.S.C. § 271(e)(2)(A), provided that any such claim is not proven invalid.
- Actavis's making, offering to sell, selling, or importing the product that is the subject of ANDA No. 207139 according to its presently indicated use would actively induce and contribute to the infringement of claims 1, 2, 4, 9, and 10 of the '251 patent and Actavis's submission of ANDA No. 207139 is an act of infringement of claims 1, 2, 4, 9, and 10 of the '251 patent pursuant to 35 U.S.C. § 271(e)(2)(A), provided that any such claim is not proven invalid.
- Except as stated herein, nothing in this Order shall affect the remainder of the parties' claims and counterclaims concerning U.S. Patent Nos. 7,598,271; 8,658,663; and 8,946,251 or any remedies (including without limitation, further injunctive relief) pertaining thereto.

Dated: \_\_\_\_\_

\_\_\_\_\_  
**Hon. Claire C. Cecchi**  
**United States District Judge**

**CERTIFICATE OF SERVICE**

I hereby certify that on November 2, 2016, I served, by Electronic Case Filing (ECF), a copy of this JOINT STIPULATION and [PROPOSED] ORDER REGARDING JOINT STIPULATION on all counsel of record who have registered for ECF notification.

/s/Anne B. Sekel  
Anne B. Sekel

# EXHIBIT 38

This site became the new ClinicalTrials.gov on June 19th. [Learn more.](#)

We will be updating this site in phases. This allows us to move faster and to deliver better services. [Show less](#)

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Trial record **1 of 1** for: NCT00786188

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## **Eight-Week Efficacy & Safety Study of Brisdelle™ (Formerly Known as Mesafem) in the Treatment of Vasomotor Symptoms Associated With Menopause**

**This study has been completed.**

**Sponsor:**

Noven Therapeutics

**Information provided by (Responsible Party):**

Noven Therapeutics

**ClinicalTrials.gov Identifier:**

NCT00786188

First received: November 4, 2008

Last updated: October 14, 2015

Last verified: October 2015

[History of Changes](#)

[Full Text View](#)

[Tabular View](#)

[Study Results](#)

[Disclaimer](#)

[How to Read a Study Record](#)

### **► Purpose**

This is an exploratory 8-week, multicenter, double-blind, randomized, placebo-controlled study of Brisdelle (paroxetine mesylate) Capsules 7.5 mg in subjects with moderate to severe postmenopausal vasomotor symptoms (VMS), defined as follows:

- Moderate VMS: Sensation of heat with sweating, able to continue activity
- Severe VMS: Sensation of heat with sweating, causing cessation of activity

Condition	Intervention	Phase
Hot Flashes	Drug: Brisdelle (paroxetine mesylate) Drug: Sugar pill	Phase 2

Study Type: **Interventional**

Study Design: **Allocation: Randomized**

**Intervention Model: Parallel Assignment**

**Masking: Double Blind (Participant, Care Provider, Investigator, Outcomes Assessor)**

**Primary Purpose: Prevention**

**Official Title:** A Phase 2, Exploratory, Eight-Week, Multicenter, Double-Blind, Randomized, Placebo-Controlled, Efficacy and Safety Study of Mesafem (Paroxetine Mesylate) Capsules in the Treatment of Vasomotor Symptoms Associated With Menopause

**Resource links provided by NLM:**

[MedlinePlus](#) related topics: [Menopause](#)

[Drug Information](#) available for: [Paroxetine](#) [Paroxetine hydrochloride](#) [Paroxetine hydrochloride hemihydrate](#) [Paroxetine Mesylate](#)

[U.S. FDA Resources](#)

**Further study details as provided by Noven Therapeutics:**

**Primary Outcome Measures:**

- Mean Change From Baseline in Hot Flash Frequency at Week 4 and Week 8 [ Time Frame: Week 4 and Week 8 ]

The number of hot flashes reported in the result table are:

- Mean change in frequency of moderate to severe VMS from baseline to Week 4
- Mean change in frequency of moderate to severe VMS from baseline to Week 8. They are both measured as hot flashes per week.

- Mean Change From Baseline in Hot Flash Severity at Week 4 and Week 8 [ Time Frame: Week 4 and Week 8 ]

A scale was not used to measure severity scores. Severity scores of hot flashes were calculated for each subject. The following formula was used to calculate severity.

$$SS = (2 \cdot F_m + 3 \cdot F_s) \div (F_m + F_s)$$

Where:

SS = severity score F<sub>m</sub> = frequency of moderate hot flashes F<sub>s</sub> = frequency of severe hot flashes The mean number of moderate and severe hot flashes that was recorded in the Run-In Period was used to calculate the baseline severity score.

**Secondary Outcome Measures:**

- Change From Baseline in Climacteric Symptoms at Week 8 [ Time Frame: Week 8 ]

The Greene Climacteric Scale (GCS) was used for this measurement. The scale has 21 questions and measures symptoms in 4 areas; these are psychological (anxiety and depression), physical, vasomotor, and libido.

The severity of the symptom was scored as: 0=none, 1=mild, 2=moderate, and 3=severe. Anxiety was determined by using the sum of scores 1 to 6, and depression was determined by using the sum of scores 7 to 11. Physical aspects were determined by using the sum of scores 12 to 18; vasomotor aspects were determined by using the sum of scores 19 to 20; and libido was determined by using the score for question 21.

The total GCS score ranges from "0" to "63" which is the sum of all the scores for the 21-symptom assessment questions in this scale. Each subject's total GCS score at baseline and at Week 8 were used to calculate change from baseline in these symptoms. The change from baseline is reported below.

- Change From Baseline in Hot Flash Composite Score at Week 4 and Week 8 [ Time Frame: Week 4 and Week 8 ]

A scale was not used for this measurement.

Composite scores of hot flashes were calculated by using the following formula:

$$CS = (2 \cdot Fm + 3 \cdot Fs)$$

Where:

CS = composite score Fm = frequency of moderate hot flashes Fs = frequency of severe hot flashes The mean number of moderate and severe hot flashes recorded in the Run-In Period was used to calculate the baseline composite score.

- Effect of Brisdelle (Paroxetine Mesylate) Capsules on Depression and Anxiety at Week 8 [ Time Frame: Week 8 ]

Depression & anxiety were measured using the Hospital Anxiety & Depression Scale (HADS).

The HADS is a scale developed to assess anxiety & depression. The HADS Scale consists of 14 Questions (7 relating to anxiety; 7 relating to depression) with possible scores ranging from 0 to 21.

The results presented below are the number of participants with abnormal HADS Scores for both Abnormal Anxiety & Abnormal Depression combined at Week 8.

- Effect of Brisdelle (Paroxetine Mesylate) Capsules on Mood at Week 4 [ Time Frame: Week 4 ]

Mood was measured using the Profile of Mood States (POMS) Questionnaire. The Profile of Moods States (POMS) is a 65-item multi-dimensional measure that provides a method of assessing transient, fluctuating active mood states. Key areas that are measured include: tension-anxiety, anger-hostility, fatigue-inertia, depression-dejection, vigor-activity, confusion-bewilderment. Responses to questions are scored with the following numerical values: Not at all = 1, A little = 2, Moderate = 3, Quite a bit = 4, Extremely = 5. A total score for a domain was obtained by summing the responses of individual items in the domain. The total POMS score can range from "65" to "335."

The percentage of participants who had a change from baseline in the total score at Week 4 is reported below.

- Effect of Brisdelle (Paroxetine Mesylate) Capsules on Improvement of Hot Flash Interference at Week 4 [ Time Frame: Week 4 ]

Interference of hot flashes was measured by using the Hot Flash-Related Daily Interference Scale (HFRDIS). The HFRDIS is a 10-item scale that measures the degree to which hot flashes interfere with 9 daily activities and the tenth item measures the degree to which hot flashes interfere with each of the other items. Subjects can score for each item on a scale from 0 to 10 where 0 = Do not interfere and a score of 10 = Completely interferes.

The measure being reported below is percentage of responders who had an improvement in HFRDIS score at Week 4 compared to baseline. A responder is defined as a subject who had an improvement in the HFRDIS score. An improvement is define as a score  $\leq 3$  on each question.

- Proportion of Clinical Global Impression (CGI) Responders at Week 4 and Week 8 [ Time Frame: Week 4 and Week 8 ]

The Clinical Global Impression Scale (CGIS) was completed by the investigator and was used to measure the severity of the VMS at any given time and the improvement from baseline. Responders were defined as subjects who achieved a score of 1 to 3 where 1 = very much improved, 2 = much improved, and 3 = minimally improved. Non-responders were defined as subjects who achieved a score of 4 to 7 where 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.

- Asses the Effect of Brisdelle (Paroxetine Mesylate) Capsules on the Interference on Sexual Functioning at Week 8 [ Time Frame: Week 8 ]

The Arizona Sexual Experiences Scale (ASEX) is a 5-item rating scale that quantifies sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. Possible total scores range from 5 to 30, with the higher scores indicating more sexual dysfunction. The sum of the scores for all 5 items was calculated.

- Proportion of Numerical Rating Scale (NRS) True Responders at Week 4 and Week 8 [ Time Frame: Week 4 and Week 8 ]

The Subject Impression Numerical Rating Scale (NRS) is an 11-point scale was used to measure how bothered a subject was by hot flashes both during the day and the night.

The measure being reported below is percentage of responders who had an improvement in NRS score at Week 4 compared to baseline. A responder is defined as a subject who had an improvement in the NRS score. An improvement is define as a score  $\leq 3$  on each question.

- Effect of Brisdelle (Paroxetine Mesylate) Capsules on BMI at Week 4 and Week 8 [ Time Frame: Week 4 and Week 8 ]

Body Mass Index (BMI) was calculated by using height in centimeters and weight in kilograms.

Enrollment: 102  
 Study Start Date: November 2008  
 Study Completion Date: June 2009  
 Primary Completion Date: June 2009 (Final data collection date for primary outcome measure)

<u>Arms</u>	<u>Assigned Interventions</u>
Experimental: Brisdelle (paroxetine mesylate) Eligible subjects will be randomized to receive Brisdelle (paroxetine mesylate) Capsules 7.5 mg.	Drug: Brisdelle (paroxetine mesylate) Eligible subjects will be randomized to receive Brisdelle™ (paroxetine mesylate) Capsules 7.5 mg. Other Names: <ul style="list-style-type: none"> <li>• Former Names: Mesafem capsules 7.5 mg or</li> <li>• LDMP (Low-Dose Mesylate salt of Paroxetine)</li> </ul>
Placebo Comparator: Placebo - Sugar Pill Eligible subjects will be randomized to receive a sugar pill.	Drug: Sugar pill Subjects will receive a sugar pill.

**Detailed Description:**

Eligible subjects will be entered into a 1-week observation period followed by a 1-week run-in period. Following completion of the run-in period, eligible subjects will be randomized to receive either Brisdelle (paroxetine mesylate) Capsules 7.5 mg or placebo in a 1:1 ratio. Study drug will be administered once daily at bedtime. Symptom assessment questionnaires will be administered at baseline and at Day 28 and Day 57 visits.

 **Eligibility**

Ages Eligible for Study: 41 Years and older (Adult, Senior)  
Sexes Eligible for Study: Female  
Accepts Healthy Volunteers: No

**Criteria**

## Inclusion Criteria:

1. Female, >40 years of age
2. Reported more than 7-8 moderate to severe hot flashes per day (average) or 50-60 moderate to severe hot flashes per week for at least 30 days prior
3. Spontaneous amenorrhea for at least 12 consecutive months
4. Amenorrhea for at least 6 months and meet the biochemical criteria for menopause
5. Bilateral salpingo-oophorectomy >6 weeks with or without hysterectomy

## Exclusion Criteria:

1. History of hypersensitivity or adverse reaction to paroxetine mesylate
2. Use of an investigational study medication within 30 days prior to screening or during the study
3. Concurrent participation in another clinical trial or previous participation in this trial
4. Family of investigational-site staff

 **Contacts and Locations**

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see [Learn About Clinical Studies](#).

Please refer to this study by its ClinicalTrials.gov identifier: NCT00786188

**Locations****United States, Florida**

Altus Research  
Lake Worth, Florida, United States, 33461

Anchor Research Center  
Naples, Florida, United States, 34102

**United States, North Carolina**

Hawthorne Research

Greensboro, North Carolina, United States, 27408

Hawthorne Medical Research, Inc.  
Winston-Salem, North Carolina, United States, 27103

#### United States, Pennsylvania

Philadelphia Clinical Research  
Philadelphia, Pennsylvania, United States, 19114

#### United States, Tennessee

Chattanooga Medical Research, LLC  
Chattanooga, Tennessee, United States, 37404

#### United States, Virginia

Virginia Women's Center  
Richmond, Virginia, United States, 23233

National Clinical Research, Inc.  
Richmond, Virginia, United States, 23294

#### United States, Washington

Women's Clinical Research Center  
Seattle, Washington, United States, 98105

North Spokane Women's Clinic Research  
Spokane, Washington, United States, 99207

#### Sponsors and Collaborators

Noven Therapeutics

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Principal Investigator:	Samuel N. Lederman, MD	Altus Research, Lake Worth, FL 33461
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Principal Investigator:	James E. Tomblin, MD	Hawthorne Medical Research, Inc., Greensboro, NC 27408
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Principal Investigator:	D. S. Harnsberger, MD	Chattanooga Medical Research, LLC, Chattanooga, TN 374
Principal Investigator:	John A. Hoekstra, MD	National Clinical Research, Inc., Richmond, VA 23294
Principal Investigator:	Robin Kroll, MD	Women's Clinical Research Center, Seattle, WA 98105
Principal Investigator:	Ashley Tunkle, MD	Anchor Research Center, Naples, FL 34102

#### More Information

Publications:

[Fugate SE, Church CO. Nonestrogen treatment modalities for vasomotor symptoms associated with menopause. Ann Pharmacother. 2004 Sep;38\(9\):1482-99. Epub 2004 Aug 3. Review.](#)

Kritz-Silverstein D, Goldani Von Mühlen D, Barrett-Connor E. Prevalence and clustering of menopausal symptoms in older women by hysterectomy and oophorectomy status. J Womens Health Gend Based Med. 2000 Sep;9(7):747-55.

Nelson HD, Vesco KK, Haney E, Fu R, Nedrow A, Miller J, Nicolaidis C, Walker M, Humphrey L. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. JAMA. 2006 May 3;295(17):2057-71. Review.

Greene JG. A factor analytic study of climacteric symptoms. J Psychosom Res. 1976;20(5):425-30.

Responsible Party: Noven Therapeutics  
 ClinicalTrials.gov Identifier: [NCT00786188](#) [History of Changes](#)  
 Other Study ID Numbers: N30-002  
 Study First Received: November 4, 2008  
 Results First Received: July 16, 2013  
 Last Updated: October 14, 2015

Keywords provided by Noven Therapeutics:

Menopause	Nonhormonal therapies
Vasomotor Symptoms	Climacteric symptoms
Hot flash	Mesafem
Perimenopause	Low-Dose Mesylate salt of Paroxetine (LDMP)

Additional relevant MeSH terms:

Hot Flashes	Serotonin Agents
Signs and Symptoms	Physiological Effects of Drugs
Paroxetine	Antidepressive Agents, Second-Generation
Serotonin Uptake Inhibitors	Antidepressive Agents
Neurotransmitter Uptake Inhibitors	Psychotropic Drugs
Membrane Transport Modulators	Cytochrome P-450 CYP2D6 Inhibitors
Molecular Mechanisms of Pharmacological Action	Cytochrome P-450 Enzyme Inhibitors
Neurotransmitter Agents	Enzyme Inhibitors

ClinicalTrials.gov processed this record on July 19, 2017

# EXHIBIT 39

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY

1	SEBELA INTERNATIONAL LIMITED,	:	
2		:	
3	Plaintiff,	:	TRANSCRIPT OF PROCEEDINGS
4		:	- Trial -
5	v.	:	MORNING SESSION
6		:	
7	ACTAVIS LABORATORIES FL, INC.,	:	
8	ACTAVIS PHARMA, INC., ANDRX	:	
9	CORP., and ACTAVIS, INC.,	:	2:14-cv-06414(CCC-MF)
10		:	Consolidated With
11	Defendants.	:	2:15-cv-06225(CCC-MF)
12	- - - - -x	:	
13	SEBELA INTERNATIONAL LIMITED,	:	
14		:	
15	Plaintiff,	:	
16		:	
17	v.	:	
18		:	
19	PRINSTON PHARMACEUTICAL INC.,	:	2:14-cv-07400(CCC-JBC)
20	SOLCO HEALTHCARE U.S., LLC, and	:	Consolidated With
21	HUAHAI US INC.,	:	2:15-cv-05308(CCC-JBC)
22		:	
23	Defendants.	:	
24	- - - - -x	:	

Newark, New Jersey  
December 12, 2016

B E F O R E:

THE HONORABLE CLAIRE C. CECCHI,  
UNITED STATES DISTRICT JUDGE

Pursuant to Section 753 Title 28 United States Code, the  
following transcript is certified to be an accurate record as  
taken stenographically in the above entitled proceedings.

S/WALTER J. PERELLI

WALTER J. PERELLI, CCR, CRR  
Official Court Reporter  
wjpcrr1975@gmail.com

A P P E A R A N C E S:

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Attorneys for Actavis Laboratories FL, Inc., Actavis

Pharma, Inc., Andrx Corp., and Actavis, Inc.

1           MR. CUNNING: Neither party has supplemented after  
2 your Honor's claim construction decision, so --

3           THE COURT: I'm very well aware of the timing in the  
4 case as well and I think this is appropriate, this is fine.  
5 And again, to the extent that there's anything that needs to be  
6 brought out in the testimony, Defendants -- excuse me --  
7 Plaintiff is afforded the opportunity to cross-examination  
8 here. But otherwise I do feel that this is appropriate. So  
9 I'm going to overrule the objections. And again, we're  
10 objecting to the demonstratives and we're not objecting to the  
11 exhibits at this point. So I think that it is fine to let them  
12 go forward.

13           Is there any other issue with respect to this witness  
14 before we go forward?

15           MR. CUNNING: I don't believe so your Honor.

16           MS. PETERSON: I guess just to be clear, I mean  
17 it's -- I certainly understand your ruling that the  
18 demonstratives can be used. However, we of course do maintain  
19 our objections and I will repeat those objections as we proceed  
20 forward with the testimony.

21           THE COURT: You may do so.

22           MS. PETERSON: Okay. Thank you.

23           THE COURT: Thank you.

24           Let's begin.

25           MR. CUNNING: Then the Defendants would like to call

1 Dr. Locker to the stand.

2 THE COURT: Yes.

3

4 B R I A N K. L O C K E R, as a witness, having been first  
5 duly sworn, is examined and testifies as follows:

6

7 THE DEPUTY CLERK: Please state your full name,  
8 spelling your last name for the record.

9 THE WITNESS: Brian Locker, L-o-c-k-e-r.

10 THE COURT: Good afternoon, or good morning.

11 THE WITNESS: Good morning, your Honor.

12 THE COURT: Good morning.

13 Okay. Good morning still.

14 All right. The witness has been sworn.

15 Let us begin.

16 MR. CUNNING: Permission to approach, your Honor?

17 THE COURT: Yes.

18 MR. CUNNING: I just need to hand the witness his  
19 binder.

20 THE COURT: Yes.

21 THE WITNESS: Thank you.

22 DIRECT EXAMINATION

23 BY MR. CUNNING:

24 Q Good morning, or good afternoon, Dr. Locker.

25 A Good morning.

1 Q Please introduce yourself to the Court.

2 A My name is Brian Locker.

3 Q And have you been retained as an expert witness for this  
4 litigation?

5 A Yes, I have.

6 Q Which parties retained you?

7 A The Defendants.

8 Q Would you please describe your educational background for  
9 the Court?

10 A Sure. I was an undergraduate student at the University of  
11 Illinois in Champaign/Urbana. My degree was in biology and in  
12 music. I received a Masters of Science in anatomy at the same  
13 institution, U of I. I went to medical school at Rush in  
14 Chicago; and I completed an Air Force -- an Air Force OBGYN  
15 residency at Keesler Air Force Base Medical Center in Biloxi,  
16 Mississippi.

17 Q After you completed your internship and residency in  
18 Keesler Air Force Base, what did you do?

19 A Well, I had received an Air Force scholarship that paid for  
20 medical school, so I served my country for four years during  
21 medical school, I served my country for four years while I was  
22 an OBGYN resident, and then I served up at KI Sawyer Force Base  
23 in the Upper Peninsular, Michigan taking care of OBGYN needs of  
24 the active duty women as well as the retirees.

25 Q Do you still practice as an OBGYN doctor?

1 A Yes. After I left the Air Force, I received an Air Force  
2 Commendation Medal and moved my practice to Rockford, Illinois  
3 where I practiced as a general OBGYN doctor for three years;

4 Then I've been at Lutheran General Hospital for the  
5 last almost 20 years now in Chicago.

6 Q Do you hold any titles at Lutheran General Hospital?

7 A Well, I'm the president of my six-doctor OBGYN group; I'm a  
8 board member of our 60-doctor larger OBGYN group called Maywood  
9 Center for Women's Healthcare; and I serve on the faculty for  
10 teaching at Lutheran General Hospital.

11 Q And can you elaborate on your teaching experience?

12 A We have a robust group of students to be taught. I teach  
13 medical students from the University of Illinois and the  
14 Chicago Medical School; I teach the residents, we have an OBGYN  
15 residency with 14 residents each year; and I also teach the  
16 family medicine residents.

17 Q What are some of the areas of instruction that you give to  
18 these students?

19 A I basically teach them in four different arenas: First is  
20 in my office. They follow me in the office. They see patients  
21 with me;

22 Then we go to the classroom where I give lectures,  
23 they give lectures to me;

24 Then we go to labor-and-delivery where they "catch"  
25 babies with me, and then we go to the operating room where we

1 do surgery together.

2 Q Do any of those areas of instruction include the treatment  
3 of menopausal patients for hot flashes?

4 A Certainly in my office where I'm seeing my patients who  
5 have these problems, as well as in the lecture hall.

6 Q One of the terms we're going to hear today is  
7 thermoregulatory dysfunction. What does that mean?

8 A It basically means that there is a dysfunction of the  
9 body's ability to control their temperature, and this typically  
10 happens in menopause, be it surgically, if it's naturally or  
11 basically drug-induced.

12 Q What are some of the symptoms that are associated with  
13 thermoregulatory dysfunction?

14 A You typically see hot flashes or hot flushes, you get night  
15 sweats. Those are the main ones.

16 Q For purposes of today, when we talk about thermoregulatory  
17 dysfunction, is that pretty much synonymous with hot flashes?

18 A Yes, it is.

19 Q Are you a member of any professional organizations that  
20 relate to the treatment of women for symptoms associated with  
21 menopause?

22 A Yes. I'm a member and a Fellow of the American College of  
23 Obstetrics and Gynecology.

24 Q And what does it mean to be a "Fellow" of the American  
25 College of Obstetrics and Gynecology?

1       A     So, there are -- we can say our society that provides  
2       references for us, publications, we have to become board  
3       certified prior to joining ACOG. But it's a very useful source  
4       for information for us.

5       Q     Are you board certified?

6       A     Yes, I am.

7       Q     And how long have you been board certified?

8       A     I was board certified as soon as I was able to be, after I  
9       finished residency and I believe that was in 1993. And I've  
10      been board certified yearly ever since.

11      Q     Plaintiff's Trial Exhibit 338 should be Tab 1 in your  
12      binder. Do you have that?

13      A     Yes, I do.

14      Q     And what is Plaintiff's Trial Exhibit 338?

15      A     This is my CV.

16      Q     Does that set forth a complete listing of your  
17      qualifications?

18      A     Yes, it does.

19      Q     Are there any updates that you'd like to make to your CV?

20      A     Well, this was last updated April of 2016, and I've  
21      recently completed the requirements for board certification for  
22      this year. So now I am board certified through 2017.

23      Q     How often in your practice are you treating women for  
24      symptoms associated with menopause?

25      A     Pretty much every day that I'm in the office, which is two

1 or three days a week.

2 Q And were you treating women for symptoms associated with  
3 menopause in the 2006 time frame?

4 A Ever since I graduated from medical school I've been taking  
5 care of women with hot flashes, through residency and pretty  
6 much every day that I'm in the office.

7 Q And just as reminder, when was that?

8 A Let's see. I graduated from residency in 1991, so  
9 basically since, through residency and beyond I've been taking  
10 care of women with hot flashes.

11 Q And what are some of the treatment options that you use to  
12 help women with hot flashes?

13 A There are basically three different options: Either using  
14 some sort of estrogen, estrogen replacement therapy;  
15 non-hormonal treatments; and then the other group as other,  
16 including herbal supplements, exercise, diet and things like  
17 that.

18 Q And what are some of the non-hormonal treatment options?

19 A We typically use the group of the serotonin reuptake  
20 inhibitors, the serotonin norepinephrine reuptake inhibitors,  
21 we use Clonidine and Gabapentin. Those are the primary drugs  
22 that we use.

23 Q You personally in your practice, what are some of the  
24 non hormonal treatment options that you have experience with?

25 A I probably have the most experience using the SSRIs, like

1       paroxetine and fluoxetine.

2       Q     Do you have personal experience prescribing paroxetine to  
3       treat hot flashes?

4       A     Yes, I've been using that for quite some time.

5               MR. CUNNING:   Your Honor, at this time Defendants  
6       would like to jointly proffer Dr. Locker as an expert in the  
7       subject of treating women with thermoregulatory dysfunction  
8       associated with hot flashes, and as one qualified to understand  
9       and interpret the prior art.

10              THE COURT:   Thank you.

11              Any objection?

12              MS. PETERSON:   No, your Honor.

13              THE COURT:   He is admitted as an expert.   Thank you.

14              MR. CUNNING:   Can we bring up -- there we go.

15              (Mr. Cunning confers with the Tech off the record.)

16       BY MR. CUNNING:

17              MR. CUNNING:   Sorry your Honor, apparently I didn't  
18       play with the Trial Tech enough.   Okay.

19       BY MR. CUNNING:

20       Q     Dr. Locker, did you form any expert opinions in the course  
21       of your work on this case?

22       A     Yes, I did.

23       Q     Can you briefly outline the subject of your testimony for  
24       the Court today?

25       A     Yes.   I reviewed the '663 Patent and the '251 Patents.

1 Q And did you look at the background art that was discussed  
2 in the '663 and the '251 Patents?

3 A Yes, I did.

4 Q And what did you conclude about that?

5 A The background art was primarily talking about the use of  
6 paroxetine and the other SSRIs as basically well-known  
7 treatments for vasomotor symptoms back in 2006.

8 Q And you were asked to look at several different legal  
9 theories with regard to the '663 and the '251 Patent?

10 A Yes, I was.

11 Q And what was your analysis of those different legal  
12 theories?

13 A Well, it shows the obviousness. I believe that the prior  
14 art does teach that paroxetine was used in the mesylate form at  
15 seven and a half milligrams, and so that the obviousness is  
16 satisfied there.

17 With regard to credible utility, if the prior art does  
18 not -- is not obvious, then the other parts of the patent  
19 basically fall apart.

20 There would not be written description and enablement  
21 because there's basically nothing new in the patent.

22 Written description. My basic summary is that the  
23 description is really nothing more than a research -- research  
24 project with a hypothesis that everything less than 10  
25 milligrams is going to work for hot flashes.

1           And then for the full scope enablement which primarily  
2     pertains to the '251 patent, that there would -- this would  
3     require undue experimentation.

4     Q    Okay. beginning with the '663 Patent, that's one of the  
5     patents that you analyzed. Correct?

6     A    Yes.

7     Q    Okay. Do you have Joint Trial Exhibit 3 in your binder?  
8     It should be Tab 2.

9           When was the priority application for the '663 Patent  
10    filed?

11    A    It was on August 4th, 2006.

12    Q    What time frame did you use for the purposes of your  
13    analysis of the validity of the patents?

14    A    It was all based on that date, on August 4th, 2006.

15    Q    How long is the '663 Patent?

16    A    It's only six -- six columns long.

17    Q    In the background section discussing the prior art, was it  
18    known at the time of the filing of the '663 Patent that SSRIs  
19    and SNRIs were known to be useful for vasomotor symptoms?

20    A    Yes, several prior arts were discussed.

21    Q    And the term "vasomotor symptoms," is that another term for  
22    hot flashes?

23    A    Yes.

24    Q    Was it known at the time that the '663 Patent was filed  
25    that paroxetine was useful to treat hot flashes?

1 A Yes. Paroxetine was -- has been used for a long time.

2 Q And was it known at the time of the patent whether any  
3 specific doses of paroxetine were useful to treat hot flashes?

4 A Yes, we have prior art to support that.

5 Q And what prior art are you referring to?

6 A For the dosages?

7 Q At the time that the '663 Patent was filed.

8 A The Coelingh reference.

9 Q Does the '663 Patent specifically cite to any clinical  
10 studies that had been done with paroxetine at any specific  
11 dosage ranges?

12 A Referring to the Stearns studies?

13 Q Yes.

14 A Yes, Stearns was referenced in 2000 and then again in 2005.

15 Q And what dosage amounts -- did the Stearns 2000 study  
16 investigate with regard to the efficacy of paroxetine for hot  
17 flashes?

18 A They used 10 milligrams and then 20 milligrams.

19 Q Does the '663 Patent discuss the use of paroxetine as a  
20 combination therapy?

21 A Yes, it does.

22 Q And does it discuss the use of paroxetine as a monotherapy?

23 A Yes, it does.

24 Q What are the differences between a combination therapy and  
25 monotherapy?

1 A Well, the monotherapy is just paroxetine by itself. The  
2 combination therapy would be using paroxetine with other  
3 things, such as SNRIs, you can use it with estrogen, you can  
4 use witness the B6.

5 Q So, after the background section of the '663 Patent, when  
6 you look into the summary of the invention and the description  
7 of the invention, how does the '663 Patent characterize its  
8 novel idea?

9 A That it -- that it basically can treat all -- that the  
10 paroxetine can be used to treat all dosages from 9.5 down to .1  
11 milligrams, and to be effective for treating hot flashes.

12 Q And did the '663 Patent include any studies that would  
13 support that claim, that all doses less than 10 milligrams  
14 would work?

15 A There were prophetic studies but there were no studies that  
16 were actually performed.

17 Q And what are the prophetic studies that you're referring  
18 to?

19 A There were two prophetic examples. Example one included  
20 the paroxetine hydrochloride in mesylate from dosage from 1 to  
21 9.5 for each of them; and then for example two, it used a lot  
22 of the other forms of the paroxetine, the anhydrous, the  
23 hemihydrate, the monohydrate forms, again using from 1 to 9.5  
24 milligrams.

25 Q What is your basis to say that these studies were never

1 conducted?

2 A Well, Dr. Richards in her testimony said that she did not  
3 believe that they were done.

4 Q I would like to turn your attention to some of the  
5 background prior art to the '663 Patent.

6 You did review the prior art to the '663 Patent?

7 A Yes.

8 Q And actually before we get there, you also looked at the  
9 '251 Patent. Correct?

10 A I did.

11 Q How did the specification of the '663 and the '251 Patent  
12 compare?

13 A They were essentially the same.

14 Q So looking at the prior art, what do you have here in this  
15 time line?

16 THE WITNESS: Your Honor, would you mind if I went to  
17 the well here?

18 THE COURT: Yes, go right ahead.

19 THE WITNESS: My eyes just seem to be...

20 THE COURT: Yes, go ahead.

21 (The Witness steps down from the witness stand and  
22 approaches the screen.)

23 A Okay. So if we use the priority date of 2006 as kind of a  
24 reference point, the first thing we should look at is the use  
25 of the paroxetine in 1997, about nine years prior to the

1 priority date.

2 Q Okay. Starting with the '447 Patent, which is Joint Trial  
3 Exhibit 1 -- if you need a copy to refer to I have it as Tab 4  
4 in your binder.

5 And what was taught about the use of paroxetine as a  
6 compound in the '447 Patent?

7 A Well, they acknowledged at this point that paroxetine was  
8 an old compound, it had been used for quite some time. The  
9 hydrochloride salt was first discussed in the International  
10 Journal of Pharmaceuticals in 1988. As of 1997, the form of  
11 the hydrochloride was commercially used in Paxil. So this is  
12 now identifying another salt of paroxetine, the mesylate form.

13 Q Did the '447 Patent disclose paroxetine mesylate?

14 A Yes, it did.

15 Q And what is this compound here?

16 A So this is the paroxetine mesylate compound.

17 Q Okay. The next reference you have in your time line here  
18 is the Lemmens reference. How did the Lemmens reference factor  
19 into your analysis?

20 A So this is approximately two years prior to the priority  
21 date, and this is basically teaching us that the mesylate form  
22 is actually preferable to the hydrochloride form because it's  
23 more highly water-soluble and it has better thermal stability.

24 MR. CUNNING: And just for the Court's benefit, that's  
25 Plaintiff's Trial Exhibit 983 in the binder.

1 Q Which pieces of art did you consider next, Dr. Locker?

2 A So, we referred -- we used as prior art the 2000 Stearns  
3 and 2005 Stearns to establish that the paroxetine was useful  
4 for treating hot flashes down to 10 milligrams.

5 Q Plaintiff's Trial Exhibit 33, Tab 5 in your binder, is the  
6 Stearns 2000 study.

7 What does the Stearns 2000 study disclose?

8 A So, the Stearns 2000 study was essentially a pilot study  
9 that was measuring the effectiveness of hot flashes down to  
10 about 10 milligrams per day, and they looked at two different  
11 study groups: The 20 milligrams and the 10 milligrams. And  
12 they were found that they thought that it was a promising new  
13 treatment for hot flashes and that it was -- it was quite  
14 effective. Not as effective as the estrogen but it was  
15 effective for treating hot flashes.

16 Q Which form of paroxetine, which salt form was used in the  
17 Stearns 2000 study?

18 A It was the hydrochloride form.

19 Q And what were the doses that they were investigating?

20 A The 20 milligrams and 10 milligrams.

21 Q What was the conclusion of Stearns regarding the evidence  
22 that paroxetine would be effective to treat hot flashes?

23 A That it was -- that it was effective down to 10 milligrams,  
24 and that -- and I think that they stated that they suggested  
25 doing more prospective randomized clinic trials in the future.

1 Q And at JTX-34, the Stearns 2005 study, can you please give  
2 a brief description of the Stearns 2005 study?

3 A Sure. The Stearns 2005 study was a much more advanced  
4 study than the Stearns 2000. It was a double-blinded  
5 randomized controlled study. It was done for multi-centers, it  
6 was published in the Journal of Clinical Oncology, a  
7 peer-reviewed journal, and it basically showed that the 10  
8 milligrams and 20 milligram dosages compared to placebo  
9 significantly reduced hot flashes.

10 Q What is a randomized double-blind crossover  
11 placebo-controlled trial?

12 A Well, this is what we consider our "Gold Standard" in  
13 medical research. This is a way to compare a drug directly to  
14 sugar pills or placebo pills. Placebo is basically people  
15 think they're getting the medication and they aren't, and they  
16 get results.

17 So in this study -- try to move to the next slide --  
18 so the next slide, this is a little bit busy but it shows the  
19 four different study groups. The first group was the placebo,  
20 and then after the first phase, the first four weeks, then they  
21 got the paroxetine 10;

22 The next group was the placebo group, and then they  
23 got paroxetine 20;

24 The third group here is they started off with the  
25 paroxetine, and then they went to placebo; and

1           The fourth group started with paroxetine and then they  
2           went to the placebo.

3           And you can see that the groups that got the drugs  
4           actually had a significant improvement in the frequency of  
5           their hot flashes to a rough equivalent of around 50, 55  
6           percent.

7           When this group switched over to the placebo, their  
8           hot flashes didn't improve so much. And the same thing the  
9           other way: The placebo groups that started didn't have much  
10          improvement. There was some improvement in the 20 milligram  
11          group here, but then when they actually went on the actual  
12          drugs they noticed a significant decrease.

13        Q   And is paroxetine known to be associated with any  
14        particular response regarding the placebo effect?

15        A   Yes.

16        Q   I'm sorry -- hot flashes: Are hot flashes known to have  
17        any particular response regarding placebo effect?

18        A   Yes, the placebo effect with hot flashes -- I'm sorry --  
19        the placebo effect with hot flashes was quite high. As you can  
20        see here, some of the groups here it was as high as 30 percent.  
21        So 30 percent of the people got better with just a placebo.

22        Q   What is the significance of designing the study as a  
23        crossover design?

24        A   Well, basically they use their own patients as a control  
25        group. So you can see -- and these patients didn't know if

1     they got the drug or if they got the placebo, that's the  
2     double-blinded part of it. So the patients don't even know,  
3     and then all of a sudden four weeks later they cross over and  
4     then you can see that -- you can see effectiveness from the  
5     placebo group to the used group. There's some pretty  
6     significant changes.

7     Q    How did the 10 milligrams dose of paroxetine compare to the  
8     20 milligram dose?

9     A    Their conclusion was they were very similar.

10    Q    Can you illustrate that with the data in the chart?

11    A    Sure. I mean, in the first group, the groups that got 10  
12    and 20 were right around 50 percent; this group didn't do quite  
13    as well at 35 percent; but the other group here at 20  
14    milligrams of paroxetine did equivalently.

15    Q    At the time that Stearns published this 2005 article, were  
16    other SSRIs and SNRIs already known to be effective for the  
17    treatment of hot flashes?

18    A    Yes. OBGY doctors were using several of the other SSRIs,  
19    basically we were using the entire group of SSRIs and also we  
20    were using the SNRIs as well.

21    Q    And what specific dose did Stearns recommend after the  
22    conclusion of this study?

23    A    Well, if you look at the side effects -- and this is what  
24    was really important -- was the side effects at 20 milligrams,  
25    and the side effects we're really talking about predominantly

1 were with the sexual side effects. The sexual side effects are  
2 decreasing arousal, decreasing desire, decreasing the ability  
3 to achieve orgasm. Those side effects all went down from 20  
4 milligrams down to 10 milligrams. So the recommendation was to  
5 go use the lower dose of 10 milligrams.

6 Q Was this a good study?

7 A Well, I think it was a well-designed study, you know, by  
8 the fact that it was randomized, placebo-controlled, it's in a  
9 peer-reviewed journal.

10 A peer-reviewed journal basically means that some  
11 journals will take any articles at all. In the peer-reviewed  
12 journals, like this journal, there's an authority figure that  
13 basically will review these articles, a respected member of  
14 their society, a respected member of that college, and they  
15 will review the articles for accuracy.

16 Q And is this the kind of article that a medical practitioner  
17 would rely upon?

18 A Yes.

19 Q And, in fact, did doctors rely upon these publications and  
20 prescribe 10 milligrams paroxetine to patients for hot flashes?

21 A Yes, we did.

22 Q And what does off -- what is off-label use?

23 A Basically, you know, the FDA will give a drug the  
24 indications that it can be used for, and if you don't follow  
25 those FDA guidelines, then it's considered off-label use. This

1 is something we do all the time.

2 Q In 2005, was paroxetine approved for hot flashes?

3 A In 2005, no, it was not.

4 Q So how were doctors prescribing paroxetine to patients for  
5 hot flashes back in that time frame?

6 A We were using Paxil, paroxetine hydrochloride, and we were  
7 just using it off-label at these dosages.

8 Q The observation that paroxetine's effect at 20 milligrams  
9 was similar compared to 10 milligrams, what does that tell a  
10 person of skill in the art?

11 A I'm sorry. Can you repeat the question?

12 Q Yes. What conclusions do you draw from the fact that  
13 paroxetine was effective at 20 and it had the same or nearly  
14 the same efficacy at a dosage of 10 milligrams?

15 A Well, that would suggest to me that you could go down lower  
16 in the dose range. And again, the goal of every medication  
17 that we prescribe is to lower the side effects and keep the  
18 effectiveness of the drug. So that certainly is a very  
19 reasonable assumption that we use, that going to a lower dose  
20 than 10 would be reasonable.

21 Q And in your review of materials in this case did you see  
22 where the patentee made any characterizations of the teaching  
23 in Stearns and whether or not it would suggest going lower than  
24 10 milligrams?

25 A Yes. When the patentee went to the doctors at the FDA,

1 that was a statement that was made to them; that they state  
2 here that they suggested that this was a new product to use a  
3 lower dose than the 10 milligrams, and because what I just  
4 said, it would be effective at decreasing the AEs, or adverse  
5 effects.

6 MS. PETERSON: Your Honor, Plaintiff just reasserts  
7 the objection that we raised earlier concerning the subject of  
8 this testimony for the same reasons.

9 THE COURT: Thank you. And that's overruled.

10 Thank you.

11 Go forward.

12 Q And, Dr. Locker, this statement comes from Plaintiff's  
13 Trial Exhibit 151 labeled an "IND."

14 What is an IND?

15 A I believe an application for a new drug.

16 Q And what is the purpose of an IND?

17 A To start the process of getting a new drug FDA-approved.

18 Q Did the patentee characterize Stearns, the Stearns 2005  
19 study to the Patent Office in the same way that it  
20 characterized it to the FDA?

21 A No, they took kind of a contrary approach, the opposite  
22 approach to the Patent Office. They stated that Stearns does  
23 not suggest that a lower dose should be used.

24 Q And in your view, how would, as a person of skill in the  
25 art, how would you read the Stearns study? Does it or does it

1 not suggest going to a lower dose?

2 A Well, as a clinician in private practice, we have patients  
3 all the time with side effects, and so if I know that it's good  
4 at 20 and it's good at 10, I think it's very reasonable if a  
5 patient is having side effects, to go lower. And so that's a  
6 very reasonable assumption; and we do this for a lot of our  
7 medications in our daily lives.

8 Q Turning back to your prior art time line, what is the next  
9 reference that you have highlighted here?

10 A So, it's the Coelingh reference performed in 2002, and this  
11 basically is setting the prior art with regard to the actual  
12 dosages. And the dosages that we're going to refer to are .2  
13 to 8.4 milligrams per day with 7.5 milligrams I think being  
14 inclusive of that.

15 Q And the Coelingh reference should be Plaintiff's Trial  
16 Exhibit 982 included at Tab 9 in your binder.

17 When was Coelingh published?

18 A So, it was published in 2002, approximately four years  
19 prior to the priority date for the '663.

20 Q Generally what does it describe?

21 A So, it's an article talking about the use of SSRIs with B6  
22 to help -- the B6 helps potentiate the medication and makes it  
23 work a little bit better so that you can lower the dosages of  
24 the SSRI, and thus, reducing the side effects of the  
25 medication.

1 Q You reviewed the file histories of the '663 and the '251  
2 Patents in this case?

3 A Yes, I did.

4 Q Was the Coelingh reference considered by the Patent Office?

5 A It was not.

6 Q Can you explain a little bit more about what you mean about  
7 the combination of B6 and the SRIs in the Coelingh reference?

8 A Again, so they used the B6 to help potentiate this  
9 medication so that you could get lower dosages and, thus,  
10 lowering the side effect profile for the patients.

11 Q And why would a person of skill in the art look to combine  
12 the Coelingh reference with the Stearns 2005 reference?

13 A Well, I think the connection would be that Stearns  
14 certainly suggests lowering the dose, and then the Coelingh  
15 reference actually teaches that the dosages are effective.

16 Q Now, you mentioned the use of SSRIs and Coelingh.

17 Does Coelingh single out paroxetine?

18 A Paroxetine is one of the drugs that are considered in the  
19 preferred group.

20 Q And does Coelingh mention the salts of paroxetine?

21 A It does not.

22 Q Does it mention that pharmaceutically acceptable salts can  
23 be included?

24 A Yes, it basically says that all the salts can be included.  
25 And certainly paroxetine mesylate would have been an obvious

1 choice because of its better solubility and it's better  
2 stability.

3 Q And how many salts of paroxetine had been approved by the  
4 FDA in the 2006 time frame?

5 A The only two salts were the hydrochloride salt and the  
6 mesylate salt.

7 Q Why would you choose the mesylate salt over the  
8 hydrochloride salt?

9 A Because the mesylate salt has better solubility.

10 Q You mentioned the use of paroxetine or an SRI in  
11 combination with Vitamin B6. Do the claims of the '251 and  
12 '663 Patent cover combination therapies?

13 A Yes, it does. I know it uses comprising language, and so  
14 it would be allowed to be used with the paroxetine.

15 Q And did the patentee admit that the claims don't exclude  
16 combination therapies?

17 A Yes. That discussion occurred at the Patent Office, the  
18 appeals for the Patent Office.

19 Q This comes from Joint Trial Exhibit 9, the file history for  
20 the application 960. What is application 960?

21 A So, this is basically an interaction between the judge and  
22 Ms. Brinckerhoff, and basically the question was:

23 Yours does not include combination therapy?

24 And Ms. Brinckerhoff said: Yes, that's correct,  
25 because of the comprising language in '663.

1 Q Was that the application for the '663 Patent?

2 A Yes, it was.

3 THE REPORTER: Excuse me, since there's a pause:

4 I heard twice "SRI." Are you just saying "SSRI" fast  
5 and I missed the first "S"?

6 MR. CUNNING: It's sometimes referred in the  
7 literature as "SSRI" and sometimes "SRI."

8 THE REPORTER: Okay. So I'll just listen closely.  
9 Thank You.

10 I'm sorry for the interruption.

11 MR. CUNNING: I'm sorry.

12 BY MR. CUNNING:

13 Q Does Coelingh disclose dosage ranges that should be used  
14 for its therapy?

15 A Yes. There were actually several examples in the Coelingh  
16 publication.

17 Q And are the dosage ranges in terms of amounts of  
18 paroxetine?

19 A They start with trazodone, and then there's a conversion  
20 factor to several different SSRIs.

21 Q And did Coelingh specifically address whether or not it was  
22 for hot flashes?

23 A Oh, yes. In the first paragraph there, it says it's a  
24 method of suppressing hot flash.

25 Q Going back to trazodone; what is trazodone?

1 A Trazodone is just another SSRI that's used.

2 Q How do you get from dosage amounts of trazodone to dosage  
3 amounts of paroxetine?

4 A Well, Coelingh teaches -- there's a table in Coelingh that  
5 has a conversion factor. So if the idea is that you use 100  
6 milligrams of trazodone, you multiply that, if it's paroxetine,  
7 to .15, and so that if you have 100 milligrams of trazodone  
8 that would be equivalent to 15 milligrams of paroxetine.

9 Q Does Coelingh explain where the conversion factor came  
10 from?

11 A It does not.

12 Q Does it provide any data or studies to support that any of  
13 these conversion factors would work?

14 A There is -- there is an example using the fluoxetine.

15 Q And that example, is that -- does it appear to be a  
16 clinical trial that actually was run?

17 A I believe.

18 MR. CUNNING: Can we pull up Plaintiff's Exhibit 82,  
19 please.

20 Can you go to page 12 of the document.

21 Bring up the comment 15, please. I'm sorry. Line 15.

22 Can you bring up that up to the end of the page.

23 Q Is this the example you were referring to, Doctor?

24 A Yes, it is. This is with fluoxetine.

25 Q What makes you think that this is a clinical study that was

1 run?

2 A Well, it states a clinical study is conducted with 12  
3 patients with hot flashes. It's a double-blinded crossover  
4 study. They have different specific periods of study, and in  
5 quite extensive detail talking about the different groups  
6 having different amounts of medications, and then they show the  
7 result. So it's a very, very detailed analysis or example, and  
8 I have no reason to believe -- not to believe.

9 Q What are some of the details that stand out to you?

10 A Again, the fact that -- the different groups, Group A is  
11 given fluoxetine with vitamin B6 for 112 days, and another  
12 group is given fluoxetine with placebo for another 112 days.  
13 And then the group -- I mean, the detail involved with this is  
14 quite extensive.

15 Q You don't know for sure that this is a clinical study that  
16 was actually run though?

17 A That's correct.

18 MR. CUNNING: Can we come back to the slide  
19 presentation, please.

20 Indulge me for a moment.

21 Walt, I should have clarified: When I said it was  
22 used both ways in the literature, they're used interchangeably

23 Why don't I just ask the Doctor.

24 Q What is the difference between the "SSRI" and "SRI" terms?

25 A Probably the correct term is "SSRI." It's a selective

1 serotonin reuptake inhibitor. I think sometimes they take out  
2 the word "selective," so it's just serotonin reuptake  
3 inhibitor.

4 The same thing for the SSNRIs that we talk about.

5 Q And when the term "SRI" as it appears in the Coelingh  
6 reference, is it your understanding that that refers to SSRIs?

7 A Yes, those two terms are interchangeable.

8 Q So then how did you calculate the dosage amount of  
9 paroxetine that would have been disclosed by Coelingh?

10 A So, there's two basic ways: Either using a weight with it  
11 or not using a weight with it. If you use a weight with it,  
12 the lower part here, the dose rates that they recommended was  
13 .02 to .8 milligrams of trazodone. You apply the conversion  
14 factor because we're specifically referring to paroxetine, .15,  
15 and then we used the average weight, what we consider the  
16 average weight of a menopausal woman of 154 pounds or 70 kilos.

17 And so the actual dosage of paroxetine per day would  
18 be .21 milligrams to a range of 8.4 milligrams, and this is  
19 inclusive of 7.5 milligrams.

20 Q Now, what is the calculation that you have at the top part  
21 of the chart?

22 A So the top part is, basically it's not as a preferred  
23 dosage rate, it's a little bit wider and it does not take into  
24 consideration the additional variable of a patient's weight.  
25 So you take out the -- the 70 kilos and you're just using a

1 conversion factor that was in claim 2 of .8 to 80 milligrams of  
2 trazodone. Just multiply it times the conversion factor of  
3 twenty-one five, then you have your range of .09 to 12. So  
4 it's a little bit wider range than the one when you use the  
5 kilograms but it's still inclusive of 7.5.

6 MS. PETERSON: Your Honor, this is just to reassert  
7 our objection, and this is the same testimony that we discussed  
8 earlier and we reserve our objection.

9 THE COURT: Thank you. And as with the last  
10 objection, it's overruled. We're going to allow it to continue  
11 for the reasons that were stated on the record. Thank you.

12 Q Dr. Locker, where did you come up with the 70 kilogram  
13 weight amount to use for the second calculation?

14 A When I look at the weights of my patients in my office, I  
15 just made an assumption of 70 kilos or about 154 -- 154 pounds.

16 Q And did you deliberately select that weight to force the  
17 calculation to include 7.5 milligrams?

18 A No, I thought that was a reasonable weight.

19 Q What happens if we change the weight up or down, is it  
20 going to exclude 7.5 milligrams?

21 A Well, if you bring the weight down, let's say you have a  
22 hundred -- a 100-pound woman, which in this day and age is not  
23 very likely, this will -- all this will do is shift it down and  
24 it will show that the dosage range is maybe a little bit lower  
25 than 8.4, but it will show that the dosage rate goes even lower

1       than 7.5.

2       Q     And what would the significance be if a dose lower than 7.5  
3       were effective?

4       A     I would presume that if it worked at 7, that it would work  
5       between 7 and 10.

6       Q     And if your 70 kilogram assumption is incorrect in the  
7       other direction, what would happen?

8       A     Well, the bottom number of .21, I think if you go up to a  
9       100 kilo woman, this only goes up to, still I believe less than  
10      1. So if you go more, then it will still include the 7.5, it  
11      will just give you a broader range.

12      Q     And 100 kilograms is about 220 pounds?

13      A     That's correct.

14      Q     How does the .09 to 12 milligram dosage range you  
15      calculated for claim 2 compare to the range of doses disclosed  
16      in the '663 Patent?

17      A     Well, the '663 Patent basically said that everything less  
18      than the antidepressant dose would be effective. So that's  
19      down from, I believe it starts from 9.5 milligrams down to .1  
20      milligrams. So this would be inclusive of that range.

21      Q     So after -- is there any other prior art that you  
22      considered in your analysis?

23      A     No.

24      Q     Okay. And considering this prior art, what did you  
25      conclude regarding the obviousness of the '663 and '251

1 Patents?

2 A Well, from all three portions, the prior art talked that  
3 paroxetine could be used for hot flashes, that the mesylate  
4 salt could be used as a salt, and that it would be effective at  
5 7.5 milligrams. So in my mind it was obvious.

6 Q And did you consider the art from the perspective of a  
7 person of ordinary skill?

8 A Yes, I did.

9 Q And did you perform any opinions about what the appropriate  
10 level of skill would be?

11 A I did.

12 (The Witness returns to the witness stand)

13 Q What is your opinion on the level of skill of one of skill  
14 in the art?

15 A That you should be at least a bachelor's degree but a  
16 medical doctor would suffice; and that they have some  
17 experience treating women with thermoregulatory dysfunctions.

18 Q And are you aware that the Plaintiff has two expert  
19 witnesses on the subject matter of the '663 and the '251  
20 Patents?

21 A Yes, I do.

22 Q And one of those witnesses is Dr. Simon?

23 A That's correct.

24 Q He also had an opinion on the level of ordinary skill?

25 A Yes.

1 Q Do you disagree with Dr. Simon's opinions?

2 A It was essentially the same as mine.

3 Q And maybe I should clarify: Do you disagree with Dr.  
4 Simon's opinions on the level of ordinary skill in the art?

5 A I don't disagree.

6 Q What are the similarities between yourself and Dr. Simon  
7 regarding the level of skill in the art?

8 A He basically agreed that they should have a medical degree  
9 and have experience with taking care of women with hot flashes.

10 Q Plaintiff also has an expert; Dr. Woodworth. Is it your  
11 understanding that Dr. Woodworth put in a definition of the  
12 level of skill, of one of ordinary skill in the art?

13 A Yes.

14 Q Do you disagree with Dr. Woodworth's analysis?

15 A His analysis, in addition to a medical degree and have --  
16 and has experience with thermoregulatory dysfunction, he also  
17 adds that they should have at least a Ph.D. in the areas of --  
18 one of these different areas.

19 Q And do you think it is necessary to have a Ph.D. in  
20 pharmacokinetics or pharmacodynamics to analyze the '663 and  
21 the '251 Patents?

22 A Well, they didn't have this included in those patents so I  
23 don't believe that it was necessary.

24 Q Do any of the claims of the '663 or '251 Patent include  
25 pharmacokinetic parameters?

1 A No.

2 Q Is there any discussion in the specification of the '663  
3 Patent of pharmacokinetics?

4 A Not that I'm aware.

5 Q What are the similarities between your definition of a  
6 person of skill and Dr. Woodworth's definition of a person of  
7 skill in the art?

8 A He also agrees that they should have a medical degree and  
9 then have some experience treating women with hot flashes.

10 Q If you were to apply Dr. Simon's and Dr. Woodworth's  
11 definition of the level of skill in the art, would it change  
12 your opinions?

13 A It would not.

14 Q Having gone through the art, without belaboring and  
15 retracing everything, would you please briefly explain to the  
16 Court how you applied the prior art to the claims at issue?

17 THE WITNESS: Would you mind if I go back to --

18 THE COURT: Whatever is comfortable. Go right ahead.

19 (The Witness steps down from the witness stand and  
20 approaches the screen.)

21 A (Continuing) So this is just a summary showing that we've  
22 basically covered all the different areas that needed to be  
23 covered. This is just going over the same thing we just  
24 basically talked about with, number one, the Stearns covers  
25 the -- teaches the use of paroxetine for hot flashes and for;

1           1a, it's with regard to the obviousness of using the  
2       mesylate salt, which again is from the Lemmens reference. And  
3       then down to the 7.5 milligrams a day is basically taught by  
4       both Stearns and by Coelingh.

5       Q   And there are more claims asserted in this case than claim  
6       1 of the '663 Patent. Correct?

7       A   That's correct.

8       Q   Did you also analyze claims 2 and 5 of the '663 Patent?

9       A   I did.

10      Q   And can you explain your comparison of claims 2 and 5 to  
11      the prior art?

12      A   Again, this is pretty similar. This is just the  
13      highlighted text that just shows the differences between claim  
14      1 and claims 2 and 5. And again, it just talks about the  
15      addition of hot flashes, and this was already taught in  
16      Stearns.

17               In 5a, talking about the mesylate salt, again in  
18      Lemmens. And there's been prior testimony in this courtroom  
19      regarding the use of -- the fact that solids are either  
20      crystalline or amorphous, and so that's already been discussed  
21      in this courtroom.

22      Q   So did you use any additional prior art for your analysis  
23      in claims 2 and 5?

24      A   I did not.

25      Q   And how does claim 1 of the '663 Patent compare to claim 1

1 of the '251 Patent?

2 A Well, the claim 1 of the '251 Patent, the entire '251  
3 Patent is just a broader patent, and so basically in the '251  
4 they say "a dosage perform of paroxetine" versus the '663  
5 Patent is specifically referring to the salt, the mesylate  
6 salt.

7 Q Are the claim elements, the differences between the two  
8 claims for the '251 Patent, are those claim elements also found  
9 in the same prior art that you addressed?

10 A Yes, it is.

11 Q And can you please briefly explain that?

12 A So again, just to show these different -- the comparisons  
13 just like we did for the '663, we're using the same prior art.  
14 And again the one is talking about -- the only difference is  
15 the difference of claim 1 of the '663 to claim 1 of the '251 is  
16 just a dosage form of paroxetine, and this is actually a  
17 broader form, so this is taught also by the Stearns reference.

18 Q Did you also analyze claims 2, 4, 9 and 10 of the '251  
19 Patent?

20 A Yes, I did.

21 Q And was there any additional art that you relied upon for  
22 claims 2, 4, 9 and 10?

23 A No, it's the exact same art.

24 MR. CUNNING: Your Honor, we're about to move into  
25 another subject line. It might be a good time to take our

1 lunch break.

2 THE COURT: That sounds fine.

3 Okay. Let's take our break now. Let's meet back at  
4 1:30. Here.

5 MR. CUNNING: Thank you, your Honor.

6 THE COURT: In an hour.

7 Thank you.

8 THE DEPUTY CLERK: All rise.

9 THE COURT: Let me just advise the witness that you  
10 remain under oath and that you're not to talk to your counsel  
11 about your testimony, or talk about your testimony, and we'll  
12 resume after lunch. But certainly you can go and enjoy lunch.

13 Go ahead.

14 THE WITNESS: Thank you very much.

15 THE COURT: Thank you very much.

16 (Witness temporarily excused.)

17 (A luncheon recess is taken.)

18 (The remainder of the day's proceedings are in a  
19 separate transcript booklet prepared by John K. Stone, Official  
20 Court Reporter.)

21 ooOoo

22

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IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY

SEBELA INTERNATIONAL LIMITED, :  
:  
Plaintiff, :  
:  
v. :  
:  
AFTERNOON SESSION

ACTAVIS LABORATORIES FL, INC., :  
ACTAVIS PHARMA, INC., ANDRX :  
CORP., and ACTAVIS, INC., : 2:14-cv-06414(CCC-MF)  
:  
Defendants. : 2:15-cv-06225(CCC-MF)  
- - - - -X

SEBELA INTERNATIONAL LIMITED, :  
:  
Plaintiff, :  
:  
v. :  
:  
PRINSTON PHARMACEUTICAL INC., : 2:14-cv-07400(CCC-JBC)  
SOLCO HEALTHCARE U.S., LLC, and : Consolidated With  
HUAHAI US INC., : 2:15-cv-05308(CCC-JBC)  
:  
Defendants. :  
- - - - -X

Newark, New Jersey  
December 12, 2016

B E F O R E:

THE HONORABLE CLAIRE C. CECCHI,  
UNITED STATES DISTRICT JUDGE

Pursuant to Section 753 Title 28 United States Code, the  
following transcript is certified to be an accurate record  
as taken stenographically in the above entitled proceedings.

S/JOHN K. STONE

JOHN K. STONE, CCR, CRR  
Official Court Reporter

1 THE CLERK: All rise.

2 THE COURT: Everyone have a seat, please.

3 Thanks for joining us.

4 THE WITNESS: Good afternoon, Your Honor.

5 THE COURT: Good afternoon.

6 MR. RIZZI: Your Honor, before Mr. Cunning resumes,  
7 I just want to note there's a new face at counsel table  
8 here, Courtenay Brincker.

9 THE COURT: Hello and welcome.

10 MR. MUSGROVE: Also from Foley.

11 THE COURT: Okay. Thank you very much.

12 Let's resume.

13 DIRECT EXAMINATION

14 BY MR. CUNNING:

15 Q All right.

16 Dr. Locker, excuse me. I'm sorry.

17 As part of your analysis did you review the file  
18 histories for the 663 and the 251 patents?

19 A Yes, I did.

20 Q All right.

21 There we go.

22 And can you please explain what you have here on  
23 this timeline?

24 A If it's okay with the Court --

25 THE COURT: Yes. You may, go wherever it's

1 comfortable.

2 A Thank you.

3 So again, we start at 2006 with a priority  
4 application being filed August 4th, 2006, and the IND was  
5 filed with the FDA in 2007.

6 Q And again, what is the IND?

7 A It's the new drug patent -- I'm sorry. I'm sorry. It's  
8 the -- it's an application for a new drug with the FDA.

9 Q And the drug at issue in that IND application?

10 A Was the paroxetine mesylate.

11 Q Is that what became Brisdelle?

12 A Yes, it is.

13 Q And up at the top, you have a Phase Two Clinical Trials.  
14 What does that refer to?

15 A So these were trials done for the use of paroxetine  
16 mesylate for hot flashes.

17 Q And had Noven done any testing prior to that time to  
18 show whether the dosage strength of 7 and a half milligrams  
19 would work?

20 A No.

21 Q What is this time period on the timeline?

22 A So between 2010, 2013, there was a significant amount of  
23 back and forth with the patent office, with the patent being  
24 rejected several times.

25 Q What do you mean by "a significant amount of

1 prosecution"?

2 A Well, they brought it to the patent office and there  
3 were multiple rejections.

4 Q Is this the source for the information on that timeline?

5 A Yes, it is.

6 Q Okay.

7 When the claims were originally filed for the 663  
8 patent did they single out the 7 and a half milligram dosage  
9 strength?

10 A Initially 7 and a half milligrams was not on the  
11 original application.

12 Q Was it listed?

13 A I believe it was one of several things that were listed  
14 there.

15 Q And how did the original com -- I'm sorry, how did the  
16 original claim compare to the specification of the 663  
17 patent?

18 A The original claims basically stated all dosages from .1  
19 up to the therapeutic dose.

20 Q And how does that compare to the disclosure in the  
21 specification of the 663 patent?

22 A I believe the specifications went from 9.5 down to a .1  
23 in intervals of half a milligram.

24 Q You mentioned, we talked about earlier today a  
25 submission of a declaration by Dr. Lippman. When did that

1       happen?

2       A    I don't remember the exact date.

3       Q    Okay.

4               Who was Dr. Lippman?

5       A    He was -- he was working for Noven as an investigator.

6       Q    And do you understand that he did some declaration  
7       during the file history of the 663 patent?

8       A    Yes, I do.

9       Q    And what was the subject of that declaration?

10      A    It was basically summarizing the results from the Noven,  
11      -- the Noven phase two trials.

12      Q    And when did those trials occur?

13      A    The -- the declaration was submitted on September 21st,  
14      2010.

15      Q    And when was the data available from that declaration?

16               Let me ask it another way.

17               Was the data available at the time that patent was  
18      filed?

19      A    Oh, no, it was not.

20               The patent was filed, the priority was 2006.

21      Q    Did Dr. Lippman in his declaration tell the patent  
22      office that the data he was submitting was not available  
23      until after the application was filed?

24      A    No, he did not.

25      Q    In your review of the file history, did the patentee

1 attach the phase two clinical study report to the  
2 declaration?

3 A No.

4 Q Did they submit the data from the phase two study report  
5 at any point in time during the prosecution?

6 A No.

7 Q After the patentee -- well, I'm sorry, at this point had  
8 the patent been allowed?

9 A No.

10 Q And how did the patentee use the Lippman declaration to  
11 respond to the rejections?

12 A Well, basically, the patentee argued that it was  
13 unexpected that the 7.5 milligrams would work, and that  
14 clinical studies were necessary to prove that it was going  
15 to work.

16 Q Okay.

17 And did the patentee amend its claims?

18 A Yes. His claims were that there was no reasonable  
19 expectation that the paroxetine would work at 7.5  
20 milligrams.

21 Q How many times did the patentee argue to the patent  
22 office that the prior art did not provide a reasonable  
23 expectation of success?

24 A I don't remember the exact number. It was a lot.

25 Q And the citations that you have here on this slide, are

1       those the different references to the patentee's arguments?

2       A    I would presume so.  I'm not absolutely certain.

3       Q    What did the patentee argue was necessary to show  
4       efficacy?

5       A    Well, the patentees basically stated that the only way  
6       to show that the drug worked was to run human clinical  
7       trials.

8       Q    Is there any clinical trial data that's reported in the  
9       663 or the 251 patent?

10      A    There's no data whatsoever.

11      Q    And is there any clinical trial data -- let me perhaps  
12      clarify the question.

13               Is there any clinical trial data reported in the  
14      663 or 251 patent for a dosage amount below 10 milligrams?

15      A    I'm not sure what you're asking.

16      Q    For -- is there any clinical trial data in the 663 or  
17      251 patents for a dose of paroxetine mesylate below 10  
18      milligrams?

19      A    There's no trial -- I mean there's no clinical data  
20      whatsoever.

21      Q    And how did that impact your analysis of the utility of  
22      the 663 patent?

23      A    Well, it wasn't -- the patent wasn't believable.

24      Q    And why is that?

25      A    Because there was no data -- there was nothing to

1 support their claim.

2 Q Earlier today you testified that the patent would have  
3 been obvious in view of the prior art?

4 A Correct.

5 Q Okay.

6 How, if the patent is obvious, how is it that you  
7 hold the opinion that the patent would not be believable?

8 A Well, the prior art, in my -- the prior art showed that  
9 it was obvious that it would work.

10 And so if that -- if you believe that, then the  
11 patent itself would not be enabled.

12 Q Did Dr. Richards conduct any testing of any of the  
13 dosage strengths that she disclosed in the 663 patent?

14 A No. She admitted that freely in her testimony.

15 Q And that's Defendants Demonstrative Exhibit 48.

16 A So, she just says here, "I don't think a clinical study  
17 had been done at that time."

18 Q The 663 patent states that all dosages less than 10  
19 milligrams down to .1 milligrams would be effective to treat  
20 hot flashes?

21 A That's correct.

22 Q Did the inventor believe that statement that was  
23 included in the 663 patent?

24 A No, she didn't.

25 Q And why do you say that?

1       A     Because in her testimony it's stated that she didn't  
2     believe that the .1 milligram, or here it says .11  
3     milligrams would likely be effective.

4               She states that she went down to that range just  
5     because her patent attorney told her to do that, to increase  
6     the range.

7     Q     And how does it affect your analysis that the inventor  
8     did not believe the statement of utility in the patent?

9     A     Well, if she -- if she put into her -- into the patent  
10    that the she's inventor of, something that is not truthful,  
11    it really makes me question the entire patent.

12    Q     What does the 663 patent rely upon to support the claim  
13    that dosages below 10 milligrams would work?

14    A     It just uses the prior art.

15    Q     And is there any data, set aside clinical study data, is  
16    there any data of any kind reported in the 663 patent to  
17    support the dosage strengths below 10 milligrams reported?

18    A     No.

19    Q     Do they report on any animal models?

20    A     No.

21    Q     Is there any in-vitro studies?

22    A     No.

23    Q     What is an in-vitro study?

24    A     A in-vitro study is where you can take cells and put  
25    them into a test tube and test the cells out.

1 Q Is the mechanism of action for SSRIs, or SSRIs to treat  
2 hot flashes, is that reported in the 663 patent?

3 A No. It's not really, no.

4 Q Is that known today?

5 A No.

6 Q And so Given that disclosure, what did you conclude  
7 regarding the utility of the 663 patent?

8 A Well, you know, if -- if it's not obvious, then it's not  
9 enabled either.

10 Q And why is that?

11 A Because there was no -- there's nothing new to  
12 support -- nothing new to support the patent.

13 Q Your analysis of the 663 patent with regard to the  
14 utility, did that apply equally to the 251 patent?

15 A Yes, it does.

16 Q And -- excuse me, the next theory that you considered  
17 was the written description requirement.

18 And what was your overall analysis of the written  
19 description requirement for the 663 and 251 patent?

20 A When I read the written description, the specifications,  
21 it looks to me like it's a research proposal with a  
22 hypothesis being that all dosages less than nine, less than  
23 10 milligrams would be effective at treating hot flashes.

24 Q Okay.

25 Why do you call it a research proposal?

1 A Well, because basically it's a research proposal, but  
2 the research was never done. It was an idea that they never  
3 did the research on.

4 Q The patentee does -- the patent, the 663 patent, for  
5 example -- ctually, can we pull up JTX 3, please.

6 And if you can turn, bring us column four, please.  
7 And bring up the material at lines 24 to 36, please.

8 Okay. Here the patent does state the dosages less  
9 than 10 milligrams are going to work. Yes?

10 A That's correct.

11 Q Okay.

12 And following this disclosure the patent includes  
13 two examples.

14 Can you bring up the next page. And the examples,  
15 please.

16 In your view, why does the inclusion of these  
17 examples not provide support that the patentee had  
18 possession of a dosage strength to treat hot flashes at 7  
19 and a half milligrams per day?

20 A Well, from my understanding, these are just prophetic  
21 examples. There was no -- there was nothing else done  
22 besides writing down these prophetic examples on a piece of  
23 paper.

24 Q Did -- the patent does in the specification list the 7  
25 and a half milligram dosage amount. Correct?

1 A It does.

2 Q And is there any significance to the listing of that 7.5  
3 milligram dosage amount?

4 A No. They just listed it in the examples, they listed it  
5 in the claims, but they just listed it there. But it  
6 doesn't have any significance. It doesn't -- it's not  
7 believable.

8 Q Can you go back to Defendants' Demonstrative 3, slide  
9 352, please.

10 Is there any indication that the patentee did  
11 anything beyond stating that the dosages would work?

12 A None that I can tell.

13 Q Did the patentee make or test any of the dosage amounts?

14 A No.

15 Q Is it your opinion for the written description  
16 requirement that the patentee is required to make and test  
17 all of the possible dosage amounts?

18 A No.

19 Q Well, what would they need to do in order to satisfy the  
20 written description requirement?

21 A Well, you know, I wasn't -- I wasn't really asked to  
22 respond to that. Because I know there's no absolute  
23 requirements when -- when you -- when you do this.

24 Q What are some of the things along the line of  
25 development that a person could have done to indicate that

1       they had possession?

2       A   Well, you could do things -- we just recently talked  
3       about, is they could do some sort of animal -- animal  
4       models.  You can do in-vitro or in-vivo studies, or you can  
5       go all the way to even doing clinical trials.

6       Q   And you reviewed Dr. Richards' testimony in preparing  
7       your analysis in this case?

8       A   Yes, I did.

9       Q   Okay.

10               In your understanding on -- for the written  
11       description requirement, what is the focus of your analysis?

12       A   The focus is the four corners of the patent.  So all the  
13       words that are on the patent.

14       Q   Okay.

15               Then why did you consider Dr. Richards' testimony  
16       if the focus of the analysis is on the four corners of the  
17       patent?

18       A   My understanding it's confirmatory.

19       Q   And what do you mean by her testimony was confirmatory?

20       A   It just -- it basically supports what -- it just  
21       supports that belief.

22       Q   How so?

23               What was it that Dr. Richards' testified that you  
24       relied upon?

25       A   Well, she did say that when the initial -- when the

1 initial patent came out, the 7.5 milligram was not even  
2 included in the original specifications, in the original --  
3 I'm sorry, the original claims.

4 Q And we did look at the original claims earlier, that  
5 claim did have a 7 and a half milligram dosage amount  
6 listed. Correct?

7 A Right. It had listed all the dosages. But it didn't  
8 specify just 7 and a half milligrams like the 663 did.

9 Q The next theory that you analyzed was the full scope  
10 enablement. And this was -- for which patent did you look  
11 at the full scope enablement?

12 A This was just analyzed for the 251 patent.

13 Q And briefly, what was your conclusion when you analyzed  
14 the 251 patent?

15 A That it would require undue experimentation to practice  
16 the full scope.

17 Q And how did you decide whether or not the  
18 experimentation was undue or routine?

19 A I applied the Wands factors.

20 Q And these are what you understand to be the Wands  
21 factors?

22 A Yes.

23 Q With respect to the breath of the claim, did you review  
24 the Court's claim construction order?

25 A Yes, I did.

1 Q And how did you consider the Court's claim construction  
2 order in analyzing the breadth of the claim of the 251  
3 patent?

4 A My understanding was that you could only consider those,  
5 -- those forms and those salts of paroxetine that actually  
6 could be -- that could actually be used and dispensed.

7 Q And did you review the 251 patent to see if it discussed  
8 what types of dosage forms could be produced and dispensed?

9 A Yes, I did.

10 Q And what did you find in the 251 patent regarding  
11 possible dosage forms?

12 A Well, there's a broad range of different forms. The  
13 oral and -- oral and non-oral dosage forms, including the  
14 parenteral, which is injection or infusion into an I-V,  
15 rectal suppositories, different topical lotion, topical  
16 cremes, topical patches.

17 Q And is that a broad or a narrow disclosure in your view?

18 A In my mind, this is a very broad, you know, a number of  
19 forms.

20 Q And what did you conclude about the nature of the  
21 invention?

22 A Well, being that it's pharmaceutical, my impression was  
23 that it's unpredictable for the untested dosage forms.

24 Q And do you have any experience prescribing  
25 pharmaceutical products that are available in various

1 different dosage forms?

2 A Everyday.

3 Q Can you give an example?

4 A One of these examples I think about is the estrogen.

5 When we use estradiol, which we use for hormone replacement  
6 therapy.

7 In the pill form the dosage form goes from .5 to  
8 one to two. When we look at the Vivelle-Dot, which is also  
9 estradiol in its natural form, the dosage range goes from  
10 .025 milligrams per day up to .1 milligrams per day.

11 So that's a huge difference factor. And when we  
12 look at the patients the same way, people, we start them on  
13 the lower end, the lower end of the pill would be .5  
14 milligrams, versus the .025 milligrams.

15 Q And those products, the tablet form and the transdermal  
16 patch form, are intended to be given to patients who are  
17 experiencing the same types of symptoms?

18 A Yes, sure.

19 For a patient with hot flashes, I normally start at  
20 a lower dose to minimize side effects. And so if a patient  
21 decides to go Vivelle-Dot or the patch, I'll start them on  
22 the lower dose, and same thing if they decide to take a  
23 pill, for whatever reason, I'll go ahead and start them on  
24 the .5.

25 Q In your experience, then prescribing medications, is it

1 a simple matter to take a drug that works at a certain  
2 strength from one route of administration and just use the  
3 same strength in a different route of administration?

4 A Well, obviously, you can't do that. I mean we're at a  
5 much, much higher dose.

6 You can't give, you know, the two milligrams in a  
7 patch form, it will be way, way too much.

8 So we're used to -- every time you change the  
9 different dosage forms you have to change the amount.

10 Q And what are some of the reasons that you need to change  
11 the dosage amount if you go to a different route of  
12 administration?

13 A Well, it depends on how the body absorbs it. The  
14 bioavailability, you know, through oral pills, you take it  
15 through your mouth, it goes into your stomach, it goes  
16 through the liver, and then it finally gets into the blood  
17 stream through that route.

18 We put it on the skin, the skin absorbs the drug  
19 and it goes right into your blood stream.

20 So depending on how -- on how it's administered  
21 will greatly effect the bioavailability of the drug.

22 Q So what did that mean for your analysis of the  
23 predictability or unpredictability of the art?

24 A So it would be unpredictable.

25 Q And did you consider the direction of guidance in the

1 specification of the 251 patent?

2 A Of course. There was essentially no guidance or  
3 direction for the 251.

4 Q Does the 251 patent include any working examples?

5 A It has -- the 251 also has the same prophetic examples  
6 as the 663.

7 Q And for the -- a tablet, for an oral tablet, is there  
8 example that they ever made even an oral tablet in the 251  
9 patent?

10 A Not that I'm aware of.

11 Q Is there an example of them making any other type of  
12 non-oral dosage form?

13 A Note that I'm aware of.

14 Q In fact, the 251 patent also covers other forms of  
15 paroxetine. Yes?

16 A Yes, it does.

17 Q And now what does that mean, the other forms of  
18 paroxetine?

19 A The different forms of paroxetines with the different  
20 salts of the solvate, the crystalline, the amorphous forms.

21 Q And do you understand that could affect the ability of  
22 the body to absorb the drug?

23 A Yes.

24 Q How does the variability in the salts or the solvate  
25 affect your analysis of the breadth of the claim?

1 A It's my understanding through the solubility of the  
2 drugs.

3 Q Does that make it more or less predictable when you're  
4 translating it from one dosage form to another?

5 A It would be more -- it would be more unpredictable.

6 Q And what is the relevant level of the skill in the art  
7 in this area?

8 A I call this neutral.

9 Q And why do you say that's a neutral factor?

10 A Well, persons of ordinary skill in the art are highly  
11 skilled people, and you think that that would make it  
12 easier. But in fact, when you look at the complicated  
13 issues that were -- are -- are encompassed here, that would  
14 make it more difficult. And so I call that a neutral  
15 factor.

16 Q How much experimentation would it have required to  
17 figure out which of the various forms of paroxetine would  
18 work at 7.5 milligrams with which of the various forms of  
19 administration?

20 A Well, if you look at all the different dosage forms and  
21 all different forms of paroxetine, it would take an  
22 extensive amount of experimentation to do all -- to do all  
23 that work.

24 Q In your view, was it required that the patentee make and  
25 test all of the possible examples?

1 A No. I think that they needed to at least -- to at least  
2 test representative samples from the different groups.

3 Q And what was the state of the art with regard to using  
4 different forms of paroxetine in different routes of  
5 administration at the time of the 663 -- I'm sorry, at the  
6 time of the 251 patent?

7 A It was basically -- there really was none.

8 Q So are there any other references that you're aware of  
9 that maybe weren't in the 251 patent that show how to do the  
10 testing necessary to figure out which ones are going to work  
11 at 7.5 milligrams?

12 A Not that I'm aware of.

13 Q Dr. Locker, earlier today you testified that the 251  
14 patent, it would have been obvious to make the 7 and a half  
15 milligram dose of paroxetine mesylate?

16 A Right.

17 Q But now if I understand you, you're saying it would  
18 require undue experimentation to practice the 521 patent?

19 A Yes.

20 Q And how -- how can you explain to the Court how you can  
21 hold those two positions?

22 A Well, when you look at the paroxetine mesylate, which is  
23 obvious here, my understanding from the law is that that  
24 would make the entire 251 patent obvious.

25 But you'd also have to do -- do experimentation to

1       also enable it. So it's not enabled. But the whole thing  
2       is obvious.

3       Q   When you're doing your undue experimentation analysis,  
4       are you focusing on the yellow dot that is the 7 and a half  
5       milligrams of paroxetine mesylate, or on the rest of the  
6       disclosure?

7       A   I'm focusing on the entire 251 patent.

8       Q   Okay.

9               And, Dr. Locker, can you just briefly summarize  
10      your opinion for the Court?

11      A   Sure.

12             So going through this, again, the obviousness, I  
13      believe the art teaches from Stearns, Lemmens and Coelingh  
14      that the patent is obvious. If it's not obvious then  
15      there's no reason to believe that the patent would -- that  
16      7.5 milligrams would work.

17             The teaching -- there's nothing new in the  
18      teaching. I mean the patent teaches nothing new.

19             The written description is nothing more than a  
20      research proposal. And as I stated, it would require undue  
21      experimentation to practice the full scope.

22      Q   And I'm going to ask just a couple more questions real  
23      quick.

24             Do you recall being asked at your deposition  
25      whether or not it would be incredible that a 5 milligram

1 dosage amount of paroxetine would be effective?

2 A Yes.

3 Q Have you given patients 5 milligrams of paroxetine.

4 A Yes, I have.

5 Q And so, if it would have been incredible that 7 and a  
6 half milligrams would work, how can you hold the opinion  
7 that it would not be incredible that 5 milligrams would  
8 work?

9 A Well, this is from my own personal experience. It, you  
10 know, in my practice, I use it and it works.

11 Q And when did that occur, what time frame were you  
12 talking about in your deposition when you were prescribing 5  
13 milligrams of paroxetine?

14 A I'm not absolutely certain. I'm not sure I actually  
15 deleted that -- I denoted that. Probably within the last  
16 few years.

17 Q After the filing of the 663 patent?

18 A I believe so.

19 MR. CUNNING: Can we pull up slide 30. I  
20 apologize. Looks like we had just a printing error.

21 BY MR. CUNNING:

22 Q At the top, do you know what the cut off language is?  
23 You see where it says, 100 milligrams of Trazodone is  
24 equivalent to 15 milligrams?

25 A Oh, this is probably -- this is probably paroxetine.

1 Q Okay.

2 Thank you.

3 At this time I pass the witness.

4 THE COURT: Thank you very much.

5 Counsel.

6 MS. PETERSON: Your Honor, we would request to take  
7 a break at this point right now, just so we can reorganize  
8 ourselves.

9 And particularly in light of the comments raised by  
10 my co-counsel this morning about the change in order of  
11 witnesses that was brought to your attention this morning.

12 THE COURT: Okay.

13 Although we did just take a long break, we can take  
14 another one.

15 MS. PETERSON: Could we take a bit?

16 THE COURT: Yes.

17 MS. PETERSON: Thank you.

18 THE COURT: Thank you.

19 THE CLERK: All rise.

20 ( After a brief recess court resumed )

21 THE CLERK: All rise.

22 THE COURT: Have a seat, please.

23 Where are we?

24 MS. PETERSON: May I proceed?

25 THE COURT: Yes.

1 CROSS-EXAMINATION

2 BY MS. PETERSON:

3 Q Good afternoon, Dr. Locker.

4 A Good afternoon.

5 Q You would agree that one of the reasons why people were  
6 looking at non-hormonal agents for treating vasomotor  
7 symptoms was due in part at least because of a need for  
8 patients who weren't able to take hormone therapy. Right?

9 A That's correct.

10 Q And certainly a large part of that population were women  
11 who were unable to take hormone therapy for their vasomotor  
12 symptoms would include patients who were suffering from or  
13 at risk of developing breast cancer. Right?

14 A Yes. That's correct.

15 Q And you understand that as of the time of the invention,  
16 tamoxifen or paroxetine was known to interfere with the  
17 efficacy of the tamoxifen. Right?

18 A That's correct.

19 Q And tamoxifen was the most commonly prescribed breast  
20 cancer therapy for patients suffering from breast cancer  
21 around the time of the invention. Right?

22 A You said paroxetine?

23 Q Or tamoxifen.

24 A Yes. I'm not absolutely certain about that. I'm not --  
25 I don't prescribe tamoxifen for my breast cancer patients.

1 So I don't know what was most commonly used or not.

2 Q But tamoxifen was certainly used as a treatment for  
3 breast cancer at the time of the invention. Right?

4 A Yes.

5 Q And you do agree that it was known as of the date of the  
6 invention to interfere -- or that paroxetine was known to  
7 interfere with the efficacy of the tamoxifen?

8 A That's correct.

9 Q And so for patients who are looking for a non-hormonal  
10 treatment for their vasomotor symptoms who are on tamoxifen  
11 to treat their breast cancer, they couldn't use paroxetine.  
12 Right?

13 A That's correct.

14 Q And a doctor or a physician such as yourself, who was  
15 looking at all of the options, the non-hormonal options at  
16 the time for their patients, if there patient was on  
17 tamoxifen, you would have picked a different type of  
18 anti-depressant or a different non-hormonal agent to treat  
19 that patient. Right?

20 A Yes.

21 Q Now, you're not aware of any other SSRIs or SNRIs or  
22 other anti-depressants that have that same drug interaction  
23 with tamoxifen. Right?

24 A I don't recall exactly. I know in my readings I believe  
25 that there were some others. But my understanding was that

1 the paroxetine was the most known for that.

2 Q Now, in your testimony that we heard earlier today, you  
3 referred to paroxetine and other low dose SSRIs and SNRIs as  
4 being effective for treating vasomotor symptoms.

5 Do you recall that?

6 A Yes.

7 Q Now if we could actually pull up Dr. Locker's  
8 demonstrative on this. I believe it's DDX 3-20.

9 A So it's here.

10 Q Can you see it?

11 A I had a hard --

12 Q There you go. Can you see it?

13 A Oh, yeah.

14 Q Okay.

15 Looking at the title of your demonstrative DDX 3-20  
16 and the information on here, you're referring to the Stearns  
17 2005 paper. Correct?

18 A Yes, I am.

19 Q And the title of your demonstrative refers to paroxetine  
20 and other low dose SSRIs/SNRIs are effective for treating  
21 hot flashes. Right?

22 A That's correct.

23 Q Now, by low dose you're referring to the lowest approved  
24 anti-depressant level dose. Right?

25 A I'm sorry. I'm distracted by this little line here. I

1 don't know how to get rid of it. There we go.

2 THE CLERK: Did it go away?

3 A I got it.

4 Okay. I'm sorry. I was distracted. Can you  
5 please repeat your question?

6 Q So, in your title, when you're referring to other low  
7 dose SSRIs/SNRIs, you're referring to the lowest approved  
8 anti-depressant level doses of those drugs. Right?

9 A That's correct.

10 Q And if we can kind of blow-up the -- starting with the  
11 second sentence of that. With Loprinzi. Go back a little  
12 bit further. I'm sorry. One line up. Start with the last  
13 yellow line. Yes. And go down about half -- all the way  
14 down to the yellow. There we go.

15 And so Stearns 2005 shown up here on the screen,  
16 these other studies with SSRIs and SNRIs, one of those is  
17 referring to the work by Loprinzi. Right?

18 A That's correct.

19 Q That would be the work concerning the SNRI drug  
20 Venlafaxine.

21 A Yes.

22 Q And you are aware of Venlafaxine is an SNRI.  
23 Right?

24 Q It's a different class of drug from SSRIs?

25 A That's correct.

1 Q So Loprinzi here is reporting, as of 2005, that the  
2 doses of Venlafaxine that were being tested were at 13.5  
3 milligrams, 75 milligrams and 150 milligrams. Right?

4 A That's correct.

5 Q And those are all anti-depressant level approved doses.  
6 Right?

7 A I don't use this drug for depression, so I'm not that  
8 familiar with it.

9 My basic understanding is that the 37.5 would be,  
10 -- is a low dose for Venlafaxine.

11 Q So, but it is still a dose approved for treating  
12 depression?

13 A That's my understanding.

14 Q And then about halfway down we see a reference to in  
15 another study, "we have evaluated the efficacy of two doses  
16 of paroxetine controlled release." That's actually  
17 referring to another study by Stearns. Right?

18 A I believe that was a 2003 Stearns. They used the low  
19 dose, the long acting paroxetine of 12.5 milligrams.

20 Q And just above that sentence there's another trial  
21 reported by the same investigators, Loprinzi, I mean that  
22 was referring to another drug, Fluoxetine. Right?

23 A That's another SSRI.

24 Q So, did you testify today that, in your opinion, from  
25 reading Stearns, that Stearns 2005 reported that paroxetine

1       could be used to treat hot flashes at 10 milligrams per day  
2       or 20 milligrams per day. Right?

3       A    Correct.

4       Q    Now, Stearns did not test any doses of paroxetine below  
5       10 milligrams per day for vasomotor symptoms. Right?

6       A    That's correct.

7       Q    And Stearns did not mention any doses below 10  
8       milligrams per day for treating vasomotor symptoms. Right?

9       A    That's correct.

10      Q    And even more specifically, Stearns did not test a dose  
11      of 7.5 milligrams per day of paroxetine for treating VMS?

12      A    That was not clearly written in Stearns. You're right.

13      Q    So clearly no reference in Stearns to a 7.5 milligram  
14      per day dose of paroxetine for treating VMS. Right?

15      A    That's correct.

16      Q    Now, you agree that SSRIs and SNRIs as a general class  
17      are known to have a number of side effects associated with  
18      them?

19      A    Yeah. Yes, very much so.

20      Q    And two of those side effects that are particularly  
21      problematic for menopausal women would be waking and sexual  
22      dysfunction. Right?

23      A    Yes.

24      Q    And those were, those two side effects in particular,  
25      those were well-known and documented to be associated with

1        paroxetine. Right?

2        A    Yes.

3        Q    So going back to your testimony earlier from Stearns,  
4        you did testify that Stearns did not report any significant  
5        side effects for the 10 milligram dose. Right?

6        A    There are still side effects. I mean if you look at the  
7        report, there are still side effects reported. They were --  
8        in -- the side effect profile decreased from 20 milligrams  
9        to 10. But even under 10 milligrams some patients were  
10       still having side effects.

11       Q    But as compared to placebo, didn't you testify that  
12       Stearns did not have any more side effects at the 10  
13       milligram as compared to placebo tested in the trial?

14       A    I don't believe I said that.

15                I know what I at least meant to say was that even  
16       at the 10 milligram dose compared to placebo, people,  
17       patients were still having side effects.

18       Q    Chris, if we could pull up the Stearns 2005 exhibits.

19                I think Dr. Locker -- Dr. Locker, you have it in  
20       your binder I believe as JTX 34.

21                We may have it as PTX 981.

22                If we could turn to 981.8. Actually .7, page 7.  
23       And let's look in the second column, the very last sentence.  
24       Second column -- second column on the right. Last sentence.

25                Stearns is reporting that they're evaluating the

1 change in status and symptoms that may be related to  
2 paroxetine. And let's go to the next page.

3 And let's pull out that whole first left column.

4 So they're considering the change in symptom status  
5 between the groups that are receiving 10 milligrams, 20  
6 milligrams and placebo. Right?

7 A That's correct.

8 Q And looking at the second full sentence on this page,  
9 Stearns reports that the only statistically significant  
10 increase in symptom status occurred on P-20. Now that's the  
11 20 milligram dose. Right?

12 A Yes, it is.

13 Q So Stearns is reporting that the only -- the only  
14 statistically significant increase in symptoms occurred with  
15 the 20 milligram dose?

16 A That's correct.

17 Q And then if we could turn to page 10.

18 And under the discussion on the left column, if you  
19 could bring up that first paragraph.

20 In the first sentence Stearns is reporting that  
21 they have demonstrated that both the 10 and 20 milligram  
22 dose was statistically and clinically significantly more  
23 effective than placebo. So that's speaking to efficacy now.  
24 Right?

25 A Correct.

1 Q And then looking at the next sentence, Stearns says  
2 P-10, the 10 milligram dose, was similar in effectiveness to  
3 the higher 20 milligram dose in producing hot flash  
4 frequency, but the toxicity profile was more favorable and  
5 women were more likely to choose continuation of P-10.

6 You see that?

7 A Yes.

8 Q So Stearns is reporting here that there were fewer side  
9 effects and fewer toxicity issues with the 10 milligram  
10 dose. Right?

11 A Yes.

12 But the toxicity, I mean the side effects weren't  
13 gone, weren't gone at 10 milligrams. I mean if the side  
14 effects are going from -- are more significant at 20, and  
15 they go down -- you have less at 10, but the patients are  
16 still having side effects at 10. And so that's what gave  
17 the suggestion that you can go lower. And this is what they  
18 stated to the FDA.

19 Q And Stearns goes on to say that women were more likely  
20 -- or women were likely to choose continuation of the 10  
21 milligram dose based on Stearns. Right?

22 A Right. That's based on the lower side effects. That's  
23 why they went to the FDA and said, we expect, you know, we  
24 have a hope of success of a lower dose to continue lowering  
25 those side effects.

1 Q And if the side effects at a particular dose are  
2 tolerable such that patients are willing to stay on the  
3 medication and don't need to discontinue, there's no reason  
4 to go lower. Right?

5 A Well, you're constantly balancing the effectiveness of  
6 the drug versus the side effects. So if the patient's at 10  
7 and not having any problems, sure, you wouldn't necessarily  
8 move them to lower.

9 But if they're still having side effects, it's  
10 reasonable, you know, this is what we do everyday in our  
11 practices with our medications.

12 Q But you do agree if the patient is not -- is not  
13 experiencing side effects, there's no reason to put them on  
14 a lower dose. Right?

15 A That's absolutely true clinically.

16 Q Now, you described at one point during your testimony  
17 the 663 patent as providing a hypothesis that all doses less  
18 than 10 milligrams per day would work. Is that right?

19 A That's correct.

20 Q Now, the claimed invention of the 663 and 251 patents,  
21 the claims don't recite treatment of vasomotor symptoms with  
22 doses of paroxetine of 10 milligrams per day or lower.  
23 Right?

24 A You're speaking specifically of the claim?

25 Q I'm speaking specifically about the claims.

1 A Yeah. The claim in the 663 just says 7.5.

2 Q So the claims for the 663 patent are limited to only one  
3 single dose of 7.5 milligrams for treating vasomotor  
4 symptoms. Right?

5 A Yes.

6 Q And the same is true with the 251 patent. The invention  
7 is directed to a single dose of 7.5 milligrams per day?

8 A I believe so. I really would feel more comfortable if  
9 we could pull out that claim just to make certain.

10 Q We can pull that up.

11 It's going to be DTX 4 in your binder, or PTX 3.  
12 If we could go to the last page. Pull out Claim 1.

13 A Yeah. I do see it here. And that is correct.

14 Q So Claim 1, in all of the claims of the 251 patent, they  
15 are committed to specifically treating vasomotor symptoms  
16 with a dose of 7.5 milligrams based on the paroxetine moiety.  
17 Right?

18 A I believe that's correct.

19 Q Now, you've actually prescribed paroxetine to some of  
20 your patients at five milligrams per day. Right?

21 A Yeah, a few of them, that they were having side effects  
22 on the 10.

23 Q And so you told those patients to -- or you prescribed a  
24 10 milligram tablet for those patients. Right?

25 A Right. I told them to cut it in half.

1 Q And at the time that you made this prescription  
2 decision, you weren't aware of any clinical studies testing  
3 the five milligram or a five milligram dose of paroxetine  
4 for treating vasomotor symptoms. Right?

5 A No. I was just doing that based on my typical clinical  
6 practice of trying to lower dosages when people are having  
7 side effects.

8 Q And in fact, there have been no clinical studies with  
9 the five milligram dose of paroxetine for treating vasomotor  
10 symptoms. Right?

11 A Well, Coelingh refers to that dosage range. So I would  
12 use a reference of Coelingh as a prior art.

13 Q Coelingh did not test a five milligram dose of  
14 paroxetine. Right?

15 A They didn't test that specific dose. But it was  
16 inclusive of their dosage range.

17 Q The Coelingh example was limited to a different SSRI.  
18 Right?

19 A Well, the Coelingh, you know, referred to, you know,  
20 using trazodone as the primary SSRI, and then they gave  
21 conversion factors to use it in the different dosages for  
22 the different paroxetines.

23 Q But you're referring to the example in Coelingh, right?  
24 For what you described as what you think is a clinical  
25 trial. Right?

1       A    The example, yes.  The example as using Fluoxetine  But  
2       my understanding is I believe that the paroxetine can be  
3       used in the same fashion.

4       Q    Okay.

5               But certainly Coelingh doesn't report any testing  
6       with a five milligram dose of paroxetine.  Right?

7       A    Well, I think it's still inclusive of the dosage range  
8       that we're referring to.

9       Q    Coelingh does not describe in its example any testing of  
10      paroxetine.  Right?

11      A    No.  Well, they gave that example for Fluoxetine.  And  
12      then they showed how to -- that was just one of -- it was  
13      just an example.  And so they showed how to use it for  
14      paroxetine in the same fashion.

15      Q    Chris, can you pull up Exhibit PTX 92.  It has a copy of  
16      the Coelingh patent.  Maybe we should just take a look at  
17      the example.

18             If you could go to page 12.  And highlight the  
19      example for us.  All the way down to the bottom, please.  
20      Thank you.

21             So this is the example that you're referring to  
22      from Coelingh.  Right?

23      A    Yes, it is.

24      Q    The example that you said you think, that you believe  
25      represents an actual clinical study that was performed.

1 Right?

2 A That's correct.

3 Q Looking at the first sentence -- or sorry. If you could  
4 pull out the third paragraph. Third and fourth paragraph,  
5 please. That start with "during an initial period in group  
6 A." Yep, that's good.

7 So what we've shown here on the screen here on PTX  
8 928, page 12, Coelingh, in its example, is reporting on a  
9 clinical study that is conducted referring to administration  
10 of Fluoxetine in combination with Vitamin B 6 and/or a  
11 placebo. Right?

12 A That's correct.

13 Q There's no reference anywhere in the example of Coelingh  
14 on page 12 of paroxetine. Right?

15 A That's correct.

16 This was just an example of the way to use the  
17 medication, the way to use that conversion factor.

18 Q So this is an example of the way to use the conversion  
19 factor. Right?

20 A Well, they have the conversion factors and they use the  
21 product, the Fluoxetine, as an example.

22 Q And what evidence do you have to show that this study  
23 was actually conducted with Fluoxetine? You don't have any.  
24 Right?

25 A I have no reason not to believe this.

1 Q You're not aware of any publications in journals  
2 describing the use of Fluoxetine in combination with Vitamin  
3 B 6 at these doses. Right?

4 A I'm not aware of them.

5 Q And certainly, if they existed, you would have cited  
6 them and relied on them in the course of forming your  
7 opinions. Right?

8 A Well, I'm just, no, I take this at face value and I have  
9 no reason not to believe that this was factual.

10 Q You understand that for a patent, when an example is  
11 drafted in the present tense, that that is what is referred  
12 to as a prophetic example. Right?

13 A My understanding of prophetic example is that it -- it  
14 was never done.

15 Q And another way to refer to a prophetic example is by  
16 use of the tense that you use in your example to describe  
17 it. Right?

18 A I'm not familiar with that legal term.

19 Q Well, if we could back up to the first sentence of the  
20 example, please.

21 The example says, "a clinical study is conducted  
22 with 12 peri-menopausal women experiencing at least 40 to 50  
23 hot flushes per week." Right. You agree with that?

24 A I do.

25 Q It does not say that a clinical study was conducted.

1 Right?

2 A That's correct.

3 Q If you could pull up the rest of the example for me,  
4 Chris, please.

5 Just like that first sentence I'm looking through  
6 the rest of this example, the way that it's described. The  
7 authors here of Coelingh say that the study is designed as a  
8 so-called double-blind, crossover study. Correct?

9 A That's correct.

10 Q The example is not drafted to say that the study was  
11 designed. Right?

12 A Yeah. I mean I know what you're saying. I just, that  
13 didn't affect my opinion. I didn't read into it as much as  
14 you are here.

15 Q But every where in the example here it's referring to  
16 the study in the present tense. You agree with that.  
17 Right?

18 A Yes. But I'm not what significance that is.

19 Q Now, looking at -- could we actually pull up both pages  
20 12 and 13 together, Chris. So we can see the full example.

21 And if you could pull out the last sentence on page  
22 12. And then the rest of page 13.

23 This example is reporting that the results show  
24 that during the period of the first 56 days the number of  
25 hot flushes experienced per day decreases substantially over

1 time. How many hot flushes were the patients experiencing  
2 before treatment?

3 A That's not clear. It wasn't stated here, as far as I'm  
4 aware.

5 Q And how many hot flushes were the patients experiencing  
6 after the treatment?

7 A It doesn't say.

8 Q And what percentage decrease in the number of hot  
9 flushes experienced per day did the patients achieve on this  
10 treatment?

11 A It doesn't -- it doesn't say.

12 Q And the same is true for group B as well. Right?

13 If we could pull that out.

14 The patent doesn't give us any information about  
15 the number of hot flushes the patients in group B had prior  
16 to treatment. Right?

17 A That's correct.

18 Q Doesn't tell us how many hot flushes the patients in  
19 group B had after the treatment. Right?

20 A It does not.

21 Q And it doesn't tell us the percentage decrease that  
22 those patients achieved through the treatment. Right?

23 A It does not.

24 Q So let's go back to what we were talking about a little  
25 while ago. And the fact that you have prescribed paroxetine

1 at a dosage of five milligrams to your patients.

2 You aren't aware of any other studies or any other  
3 information concerning a five milligram dose of paroxetine  
4 other than this example that we just walked through of  
5 Coelingh. Right?

6 A None other -- that's correct.

7 Q So even without a clinical study specifically testing a  
8 dose of five milligrams of paroxetine for treating VMS, you  
9 wouldn't find it incredible that a five milligram dose could  
10 be effective to treat your patients. Right?

11 A No, that's -- it was obvious, in my mind, you know, not  
12 using the legal term, but as a doctor, it was kind of  
13 obvious that it works at 20, it works at 10, there's no  
14 reason to believe it wouldn't work, you know, it wouldn't  
15 work lower.

16 Q So no reason to believe that it wouldn't work at five?

17 A That was my -- as a clinician, that's what I felt. And  
18 it may not, it may. In some people it will.

19 Q Now, you agree that -- and I think in your words you  
20 said it was well-known before the date of invention that  
21 paroxetine as an active agent was effective for treating  
22 vasomotor symptoms. Right?

23 A Right. In the form of paroxetine hydrochloride and  
24 Paxil.

25 Q Now, you reviewed the file history of the 663 patent in

1 the course of -- in order to prepare for your testimony.

2 Right?

3 A I did.

4 Q If we could pull up Dr. Locker's demonstrative DDX 3-41.

5 This is the timeline that you prepared for the  
6 prosecution of the 663 and the 251 patents. Right?

7 A Yes, it is.

8 Q And you also touched briefly on this, but we're in  
9 agreement here that the patentee submitted information to  
10 the TPO during prosecution of the 663 patent concerning the  
11 phase two clinical trial study for the 7.5 milligrams per  
12 day dose of paroxetine. Right?

13 A That's correct.

14 Q And that was provided to the TPO in the form of  
15 declaration submitted by Dr. Lippman?

16 A That's my understanding.

17 Q And it was also referenced in the amendment and in the  
18 remarks provided to the TPO at the same time as well.

19 Right?

20 A That's my understanding.

21 Q But you don't have that referenced here on the timeline.  
22 Right?

23 A I think the timeline had a part that came out when you  
24 -- when you use it.

25 Q Oh, sure. Yes. You had an animation --

1 A Right.

2 Q -- and I think it extended, just make a little red box  
3 over that period of significant prosecution, is that what  
4 you're referring to?

5 A This is what I'm referring to.

6 Q Do you recall the date that -- the date that the Lippman  
7 declaration was submitted to the TPO, that was on September  
8 21st, 2010. Right?

9 A I don't recall exactly, but I will take your word for  
10 it.

11 Q It's on your demonstrative number 44, if you want to  
12 confirm.

13 A I'll take your word for it.

14 Q Lippman declaration submitted September 21st, 2010.

15 Okay. So let's go back to the timeline,  
16 Demonstrative 41.

17 So we can agree then that the Lippman declaration  
18 was provided to the TPO on September 21st, 2010. Right?

19 A That's correct.

20 Q I actually, just so we can have a picture of it, maybe  
21 we could put that up there. Chris, can you -- that extra  
22 demonstrative that we sent to you.

23 So the Lippman declaration that was submitted to  
24 the TPO with a phase two clinical trial data, that was  
25 provided to the TPO on September 21st, 2010. Right at the

1 time that you described as the period of significant  
2 prosecution. Right?

3 A That's right.

4 Q Okay.

5 And just looking how this fits in with the rest of  
6 the time frame here, the Lippman declaration with the  
7 clinical -- phase two clinical data, that was submitted to  
8 the TPO years before the 663 patent issued. Right?

9 A That's correct.

10 Q And it was submitted to the TPO before the 251 patent  
11 issued as well. Right?

12 A I'm sorry, I kind of lost you there.

13 Q The Lippman declaration with the phase two clinical  
14 trial data --

15 A Okay.

16 Q -- that was submitted to the TPO before the 251 patent  
17 issued. Correct?

18 A That's correct.

19 Q And just for the record, I think we have this marked as  
20 Plaintiff's Demonstrative Number PDX 3.

21 And you're also aware from your review of the file  
22 history of the 663 patent that the invention that was under  
23 consideration, that was submitted to the Patent Trial and  
24 Appeal Board. Right?

25 A Eventually, after it had been rejected several times.

1 Q And the Patent Board of Appeals had the opportunity to  
2 consider whether the claimed invention of using 7.5  
3 milligrams per day of paroxetine to treat thermoregulatory  
4 dysfunction, the board had an opportunity to consider  
5 whether that invention was obvious over the prior art.  
6 Right?

7 A They did.

8 Q And they considered the Stearns prior art?

9 A Stearns was included, yes.

10 Q And the patent office ultimately determined that the  
11 claims were not obvious. Right?

12 A That's correct.

13 Q And permitted the patent to grant. Right?

14 A That's correct.

15 Q Now, I think you -- we can take this down now.

16 I think you testified earlier that the patentee did  
17 not submit the actual phase two clinical trial results to  
18 the patent office. Was that your testimony?

19 A That's my understanding, yes.

20 Q You were referring to the actual report documenting the  
21 clinical trial results. Is that right?

22 A Yes.

23 Q Could we pull up PTX 991, please.

24 So this is a copy, the entire copy of the Lippman  
25 declaration. Right?

1 A Yes. I identified it.

2 Q Okay.

3 If you could take a look at page 3, paragraph  
4 seven, the first few sentences.

5 This declaration here from Dr. Lippman is reporting  
6 on a phase two clinical trial of Noven's paroxetine product  
7 being conducted as an exploratory, eight week, multi-center,  
8 double-blind, randomized placebo controlled efficacy and  
9 safety study that evaluated paroxetine mesylate in the  
10 treatment of vasomotor symptoms associated with menopause.  
11 Right?

12 A That's correct.

13 Q And that would be the 7.5 milligram dose that we're  
14 talking about in this litigation. Right?

15 A Yes.

16 Q So this is referring to an actual phase two clinical  
17 trial that actually occurred. Right?

18 A I have no reason to believe it didn't.

19 Q Okay.

20 If you could go to page 4 of the declaration. I'm  
21 looking at paragraph nine. If you could get paragraph nine  
22 and the table below it.

23 The declaration is reporting in paragraph nine the  
24 actual percentage decrease and the frequency of moderate to  
25 severe hot flashes in women at weeks four and weeks eight as

1 compared to the placebo versus treatment. Right?

2 A That's correct.

3 Q And so it's reporting an actual -- an actual number for  
4 the percentage of number of hot flashes that were decreased  
5 in these women who are on the treatment as compared to  
6 placebo. Right?

7 A That's correct.

8 Q So 37.3 percent lower at week four and 42 -- 42.2  
9 percent fewer hot flashes at week eight. Right?

10 A Yes.

11 Q Let's go to page -- page 5, the next page.

12 Actually, you know what, I think if we can keep  
13 pages 4 and 5 side-by-side.

14 Let's show paragraph 10 from page 4 along with the  
15 table that continues onto page 5. For reference here, we're  
16 looking at PTX 991, pages 4 and 5 of the document.

17 So here in paragraph 10, Dr. Lippman is reporting  
18 on more results from the clinical trial. Right?

19 A That's correct.

20 Q And here he's reporting on the actual percentage  
21 decrease in severity of hot flashes experienced by the  
22 patients on treatment versus placebo. Right?

23 A That's correct.

24 Q And then let's take a look at paragraph 11.

25 In paragraph 11 Dr. Lippman is reporting additional

1 data concerning the percentage of overall responders on  
2 treatment. Right?

3 A Yes.

4 Q So with regard to overall responders there was a larger  
5 percentage in the treatment group as compared to placebo.  
6 Right?

7 A That's correct.

8 Q Okay.

9 Let's take a look at paragraph 12. The last few  
10 lines. Okay. That's fine.

11 If you could highlight the last three lines for me.  
12 Starting with the clinical trial results. Yep.

13 So paragraph 12 concludes that the clinical trial  
14 results as a whole showed that paroxetine mesylate at 7.5  
15 milligrams per day based on the paroxetine moiety was safe,  
16 well-tolerated and more effective than placebo in the  
17 treatment of vasomotor symptoms.

18 So you don't have any reason to doubt this  
19 statement. Right?

20 A I don't.

21 Q So the phase two clinical trial data submitted to the  
22 patent office confirms that a 7.5 milligram -- confirms that  
23 a 7.5 milligrams per day dose of paroxetine is effective for  
24 treating hot flashes and vasomotor symptoms. Right?

25 A Right.

1 I think the issue is that the patent office didn't  
2 know the timing of the clinical trials.

3 Q But you don't dispute that the clinical trial shows and  
4 confirms that the 7.5 milligrams per day dose was in fact  
5 effective for treating vasomotor symptoms?

6 A I agree with you.

7 Q Now, the patent office never questioned the utility of  
8 using paroxetine at 7.5 milligrams per day to treat  
9 vasomotor symptoms. Right?

10 A I don't specifically recall that. If you could  
11 remind -- refresh my memory on this.

12 Q It didn't happen.

13 A Okay.

14 Q I just want to make sure that you agree with my  
15 understanding as well.

16 A I just can't -- I just don't recall.

17 Q So you have no recollection of there being any rejection  
18 by the patent office on the grounds of utility. Right?

19 A I just don't recall.

20 Q So we were just talking about the prosecution of the 663  
21 patent. You reviewed the 251 prosecution history as well.  
22 Right?

23 A Yes.

24 Q And you're not aware or you -- you are aware that the  
25 TPO never rejected the claims of the 251 patent for lack of

1 enablement. Right?

2 A That's my understanding.

3 Q Now, you would also agree that hot flush treatments may  
4 only be assessed through patient diaries. Is that right?

5 A Well, if a patient comes in and tells me she's having  
6 hot flashes, I'll believe her.

7 Q Okay.

8 But that certainly, it's a subjective indication by  
9 the patient as to whether they are experiencing relief from  
10 their hot flash symptoms. Right?

11 A Yes.

12 Q You don't take a blood test to measure the level of the  
13 drug in the patient to see if they're responding to the  
14 treatment to alleviate their hot flash symptoms. Right?

15 A I'm not aware of that.

16 Q So when Dr. Richards came up with the invention of using  
17 7.5 milligrams per day of paroxetine to treat vasomotor  
18 symptoms, she couldn't have tested that invention through  
19 any in-vitro assay. Right?

20 A Not that I'm aware of.

21 Q Or in any animal studies?

22 A No, I think those were just examples of things that  
23 could be done, you know, potentially, if you want to  
24 consider anything. Because nothing was done.

25 Q Yes.

1 But those types of studies, in-vitro studies and  
2 animal studies, they're not appropriate for testing the  
3 potential efficacy of treatment for vasomotor symptoms.  
4 Right?

5 A Well, I don't know. I've never really -- I've never  
6 really considered that.

7 Q Because there aren't any. Right?

8 A Well, I wasn't asked to consider that.

9 Q You're not aware of any in-vitro test for assessing the  
10 efficacy of vasomotor symptom treatment. Right?

11 A That's correct.

12 Q You're not aware of any animal models either. Right?

13 A No. I can't imagine a rabbit sweating and measuring,  
14 asking the rabbit if she's having hot flashes.

15 Q Now, you reviewed the deposition testimony of Dr.  
16 Richards. Right?

17 A I did.

18 Q And you referred -- I think you referred to some of that  
19 today in your testimony as well?

20 A Yes.

21 Q And it was the testimony about whether she thought that  
22 a dose of .1 milligrams of paroxetine was likely to be  
23 effective.

24 Do you recall that?

25 A Correct.

1 Q But you did review her whole transcript. Right?

2 A I believe so.

3 Q And so you're aware that Dr. Richards also testified  
4 that she did think that three milligrams per day, all the  
5 way up to 9.5 milligrams per day, would be effective.  
6 Right? You remember that?

7 A That's correct. I do remember that.

8 Q And you recall that Dr. Richards also testified that she  
9 personally thought that 7.5 milligrams per day would work at  
10 the time that she arrived at the claimed invention. Right?

11 A I do remember that.

12 Q Moving focus a little bit, let's talk about some dosage  
13 forms of paroxetine.

14 The only dosage forms of paroxetine that you are  
15 aware of are oral dosage forms. Right?

16 A Yes.

17 Q You've never prescribed a non-oral dosage form?

18 A No.

19 Q You're not aware of the existence of any non-oral dosage  
20 forms?

21 A That's correct.

22 Q Can't prescribe one for a patient?

23 A Not that I'm aware of.

24 Q So all dosage forms of paroxetine that are currently  
25 used, they're all oral?

1 A Currently, yes.

2 Q And you would also agree that there were different  
3 dosage forms of paroxetine known in the art at the time of  
4 the invention. Right?

5 A You mean the different salts and things like that?

6 Q Yes.

7 A Yes.

8 Q So, for example, you referred to the Stearns  
9 publications and that described dosage forms of paroxetine.  
10 Right?

11 A That's correct.

12 Q And you also referred to Paxil, that's another dosage  
13 form of paroxetine?

14 A Yes.

15 Q It's paroxetine hydrochloride?

16 A Correct.

17 Q And there's also pexeva, you're familiar with that one?

18 A Not as much. I don't use it. But I know about it  
19 through my work in this case.

20 Q So that's another oral -- or that's another oral dosage  
21 form of paroxetine mesylate. Right?

22 A Correct.

23 Q And you're also familiar or you've heard of the product  
24 Celexa?

25 A I have heard of that.

1 Q And that's another dosage form of paroxetine that's  
2 available. Right?

3 A Yes.

4 Q And those were all known before the date of the  
5 invention. Right?

6 A That's correct.

7 Q And they all have therapeutic activity even though they  
8 may be made of different salts of the paroxetine. Right?

9 A Yes.

10 Q Now, you talked a little bit about the -- actually, if  
11 we could pull up Dr. Locker's demonstrative, DDX 3-64. And  
12 focusing in on your explanation of the breadth of the  
13 claims. So right column, the top box, on the last line.  
14 The last two lines where it says with paroetine parentheses,  
15 "Solvates, crystalline and amorphous forms."

16 So in your opinion this was part of your analysis  
17 as to the breadth of the claims as to be considered under  
18 the Wands factors for enablement. Right?

19 A Yes.

20 Q And you agree that -- bear with me one second.

21 You would agree with me that the therapeutic  
22 activity of a paroxetine salt is actually based on the  
23 paroxetine moiety or the paroxetine free base. Right?

24 A That's my understanding.

25 Q That's the active agent once it enters into the body?

1 A That's correct.

2 Q So the salt actually is not part of what causes the  
3 therapeutic activity. Right?

4 A That's correct.

5 Q And you would also agree with me that Paxil is  
6 paroxetine hydrochloride?

7 A It is.

8 Q And Pexeva and Brisdelle, those are paroxetine mesylate?

9 A That's correct.

10 Q And I think we covered this previously, but you agree  
11 that paroxetine hydrochloride is actually much less soluble  
12 in paroxetine mesylate. Right?

13 A Yes, I've learned that since my deposition.

14 Q And despite that difference in solubility, and its  
15 potential impact on bioavailability, they're both  
16 therapeutically effective. Right?

17 A That's correct.

18 Q Both approved by the FDA for treating the various  
19 diseases they're indicated for. Right?

20 A That's correct.

21 Q Despite the fact they're made from different salts with  
22 different solubilities?

23 A That's correct.

24 Your Honor, would it be okay to take a bathroom  
25 break?

1 THE COURT: Yes. Certainly.

2 We're going to take a five minute break.

3 THE WITNESS: Thank you so much.

4 THE COURT: Certainly. Not a problem.

5 THE CLERK: All rise.

6 ( After a brief recess court resumed ).

7 THE CLERK: All rise.

8 THE COURT: Have a seat.

9 Let's continue.

10 MS. PETERSON: Thank you.

11 THE COURT: Thank you.

12 BY MS. PETERSON:

13 Q So, just to close the lid on what we were just talking  
14 about, we were talking about paroxetine hydrochloride and  
15 paroxetine mesylate. Right?

16 A Yes.

17 Q Okay.

18 Let's -- Chris, let's pull up Exhibit PTX 977.

19 You should have a copy of that in your direct  
20 binder.

21 Do you have it? We'll put it up on the screen for  
22 you as well.

23 But PTX 977, this is a copy of the approved  
24 labeling for Pexeva. Right?

25 Pull up, look at the next page, Chris.

1                   Oh, so it may not have it right here on the page,  
2           but you do recognize this as the exhibit that was attached  
3           to your report for the Pexeva approved labeling. Right?

4           A    I'll take your word for it.

5           Q    Okay.

6                   Well, we can take -- go ahead and look at under  
7           description trade name. If you can pull that up.

8                   It refers to paroxetine mesylate. Yes. If you can  
9           highlight that there.

10                  So paroxetine mesylate, that's Pexeva. Right?

11          A    Okay.

12          Q    You agree with me. Right?

13          A    I'll take your word for it.

14          Q    Do you have any reason to doubt that the approved salt  
15           of paroxetine that's used in the Pexeva product is  
16           paroxetine mesylate?

17          A    No, I know that. I just don't see the name Pexeva here.

18          Q    Okay.

19                  But it is referring to paroxetine mesylate here.  
20           Right?

21          A    I understand that, yes.

22          Q    Okay.

23                  So let's take a look at page 19. Go down to the  
24           bottom, and let's take a look at the section on dosage and  
25           administration.

1           The Pexeva labeling here, PTX 977, indicates that  
2           Pexeva is approved for major depressive disorder. Right?

3           A    That's correct.

4           Q    And it's stating that Pexeva paroxetine mesylate should  
5           be administered as a single daily dose, with or without  
6           food, usually in the morning, and that the recommended  
7           initial dose is 20 milligrams per day. Right?

8           A    That's correct.

9           Q    So Pexeva is approved for treating major depressive  
10          disorder at 20 milligrams per day. Right?

11          A    Yes.

12          Q    Okay.

13                Let's take a look now at the Paxil labeling, which  
14          is also in your binder at PTX 989.

15                THE COURT: You know what, it's one from the back.

16          BY MS. PETERSON:

17          Q    And if we could turn to page 32, please.

18                Let's again focus on that dosage and administration  
19          section for major depressive disorder.

20          A    Okay.

21          Q    You have it?

22          A    Yes.

23                What was your question?

24          Q    So Paxil is paroxetine hydrochloride. Right?

25          A    That's correct.

1 Q And it's approved for major -- for the treatment of  
2 major depressive disorder, just like Pexeva. Right?

3 A That's correct.

4 Q And the recommended initial dose of Paxil for treating  
5 major depressive disorder is 20 milligrams per day. Right?

6 A That's correct.

7 Q And that's the same recommended initial dose as Pexeva  
8 for major depressive disorder as well. Right?

9 A Yes.

10 Q And is it your understanding that actually for all of  
11 the indications for which Paxil and Pexeva are approved are  
12 all approved and used at the same dosages?

13 A Again, I don't -- I don't typically use Pexeva, so I  
14 really can't comment on Pexeva. I mean as far as in  
15 clinical use, I don't use this.

16 Q Okay.

17 Chris, can you pull up Exhibit PTX 982.

18 That's the Coelingh patent application that we  
19 talked about earlier. Right?

20 This is Coelingh. Right?

21 A Yes.

22 Q PTX 982?

23 A Yes.

24 Q Now, you understand Coelingh to state that by using  
25 Vitamin B compounds, SSRIs can be used to treat hot flashes

1 at a lower dose. Right?

2 A Yes.

3 Q So in other words, by co-administering Vitamin B you can  
4 use a lower dose of the SRI to achieve the same effect that  
5 you would get with a higher dose of the SRI. Right?

6 A That's correct.

7 Q So it's a combination therapy?

8 A Correct.

9 Q Now, Coelingh does not suggest that paroxetine alone  
10 could be used to treat vasomotor symptoms at 7.5 milligrams  
11 per day. Right?

12 A That's my understanding.

13 Q And while it describes range, there's no mention  
14 specifically of 7.5 milligrams dose of paroxetine anywhere  
15 in the patent. Right?

16 A That's correct. It's inclusive.

17 Q It doesn't use the number 7.5?

18 A No, it does not.

19 Q And in fact, Coelingh doesn't mention paroxetine  
20 mesylate either. Right?

21 A That's correct.

22 Q If you could take a look at page 10, please. Top  
23 paragraph.

24 If you can highlight that entire first sentence,  
25 the first four lines.

1                   So here on page 10 of the Coelingh patent  
2           application it's described that the SRIs that can be  
3           employed and then it provides a list of 12 different SRIs.  
4           Right?

5           A    Yes.  I think there's an SSNRI as wel there Venla --

6           Q    Venlafaxine?

7           A    Yes.  Thank you.

8           Q    Now, Trazodone that's not an SSRI or SNRI.  Right?

9           A    It's a rather -- it's kind of a combination drug.

10          Q    Is it referred to as an atypical anti-depressant?

11          A    Yes.

12          Q    So, out of these 12 anti-depressants that are referenced  
13          here in page 10 of Coelingh, you're aware that Citalopram,  
14          the first one listed there, was also being tested prior to  
15          the date of invention for treating hot flashes.  Right?

16          A    I'm not aware of that.  I'm just not aware of it.

17          Q    What about Fluoxetine -- you're aware Fluoxetine was  
18          being tested for treating vasomotor symptoms before the date  
19          of the invention.  Right?

20          A    That was outside of my scope.  I mean I didn't  
21          investigate that as part of the prior art.

22          Q    But you're aware that that was going on.  Right?

23          A    No.

24          Q    Okay.

25                   We actually talked about that earlier today.  Maybe

1 we can pull back up again. I think it was PTX 982.

2 A I know other drugs were being used by physicians. I  
3 know we talked about that.

4 But I'm not aware of any specific studies that were  
5 being done at that time.

6 Q Do you have the Stearns 2005 exhibit that you can pull  
7 up? Or actually -- okay. Great.

8 Or it might be easier, how about we just go back to  
9 Dr. Locker's demonstrative DDX 3-20. Can you do that,  
10 Chris?

11 And about -- a few lines below the yellow  
12 highlighting -- keep going, keep going. That's fine. Yes.

13 Right after the end of your yellow highlighting  
14 there, you see a sentence there about Lorprinzi comparing  
15 three doses of Demovaxine. Right?

16 A Yes.

17 Q So you'd agree Demovaxine was being studied?

18 A Yes, I forgot that.

19 Q And the same with Fluoxetine, that's mentioned here as  
20 well. Right?

21 A Yes, ma'am.

22 Q In a separate trial by the same investigators  
23 Fluoxetine was modestly more effective than placebo in  
24 reducing the hot flash compository as well. Right?

25 A Yes.

1 Q So let's go back to Coelingh 92.

2 Now, you did review those Loprinzi papers that are  
3 referenced all throughout the Stearns papers as well.  
4 Right?

5 A I did for my original report.

6 Q Okay.

7 A I didn't use them as much for the direct.

8 Q So you considered them in the course of forming your  
9 opinions seated in your report but you didn't discuss them  
10 today?

11 A That's correct.

12 Q So can we go back to that first paragraph again.

13 So Fluoxetine was being studied for treating  
14 vasomotor symptoms before the date of the invention. Right?

15 A Yes.

16 Q Paroxetine was as well?

17 A That's correct.

18 Q Same with Venlafaxine?

19 A Yes.

20 Q And Sertraline, that was being investigated for the  
21 treatment of vasomotor symptoms before the date of the  
22 invention as well. Right?

23 A I'm not aware of that study.

24 Q And Mirtazapine -- Mirtazapine was also being studied?

25 A I didn't see that in my references.

1 Q Okay.

2 MS. PETERSON: Your Honor, I have another exhibit  
3 I'd like to use with the witness.

4 THE COURT: Yes. Bring it right up.

5 A Thank you.

6 Q So, Dr. Locker, I just handed you a copy of PTX 979.

7 Chris, can you pull that up.

8 And if you could just focus on all the way at the  
9 top, the dates, down to the title and author.

10 So, Dr. Locker, you recognize this as the Loprinzi  
11 article published in 2005 that you reviewed in the course of  
12 your work on this matter. Right?

13 A I do.

14 Q Okay.

15 So you are familiar with it, you remember reviewing  
16 it?

17 A I do now.

18 Q Okay.

19 So let's take a look at page 3.

20 So we agree this was a review article published by  
21 Loprinzi in 2005 before the date of the invention. Right?

22 A Yes.

23 Q Okay.

24 And there's a section here, you know, he's  
25 reviewing the various non-hormonal treatments for vasomotor

1 systems that were in investigation at the time. Right?

2 A Yes.

3 Q And actually, if we could go back one page.

4 He's reporting on some results with an agent called  
5 Belergel. Right?

6 A Yes.

7 Q And going to the next page, he's got some results for a  
8 drug called Clonadine. You're familiar with that one.  
9 Right?

10 A Yes.

11 Q So you know there were studies with Clonadine as of the  
12 date of the invention. Right?

13 A Yes.

14 Q And if we could focus in on, there's another section  
15 titled "Newer anti-depressants," this would be the SSRIs and  
16 the SNRIs that we've been discussing. Right?

17 A That's correct.

18 Q And in here Loprinzi is reporting on studies with  
19 Venlafaxine and paroxetine at the bottom of the first  
20 paragraph?

21 A Yes.

22 Q Turn to the next page, please. Bottom last paragraph in  
23 the left column.

24 Loprinzi is reporting on a study with Fluoxetine  
25 for treating vasomotor symptoms here. Right?

1 A That's correct.

2 Q Next column, second paragraph. Yep.

3 Here Loprinzi is reporting on the results of a  
4 trial testing Sertraline for testing vasomotor systems.  
5 Right?

6 A Yes.

7 Q And in the next paragraph, Loprinzi is reporting on  
8 results with two other anti-depressants, Mirtazapine and  
9 Citalopram. Right?

10 A That's correct.

11 Q So all of these SSRIs and SNRIs were under investigation  
12 by researchers in the field as of the date of the invention  
13 as possible non-hormonal treatment for vasomotor symptoms.  
14 Right?

15 A That's correct.

16 Q Now, going back to the Coelingh patent, PTX 982, please.  
17 If you could go back to the same page we were on.  
18 I think it was page 10.

19 And looking at that group of SRIs.

20 So I think we just decided here that a number of  
21 these SRIs in addition to paroxetine were actually in  
22 investigation at the time for treating hot flashes. Right?

23 A Yes.

24 Q It wasn't just paroxetine?

25 A That's correct.

1 Q And there's nothing else in the Coelingh patent that  
2 tells a person of skill in the art to choose paroxetine over  
3 any of these other SRIs. Right?

4 A No. They just gave a list of all the SSRIs and you can  
5 choose one.

6 Q And in fact the only place where Coelingh actually  
7 singles out a particular SRI as an example with Fluoxetine  
8 Right?

9 A That's correct.

10 Q Let's take a look at Dr. Locker's demonstrative, I think  
11 it's 3 - DDX 3 -- let's try 36.

12 Nope. How about 33.

13 31, please.

14 Now, these were the calculations that you were  
15 describing earlier using what's called the Traeseno (sp)  
16 conversion factor in Coelingh. Is that right?

17 A Yes, it is.

18 Q So for your calculation, down at the bottom, for the  
19 range of 0.02 to 0.8 milligrams of Trazodone equivalent per  
20 kilogram per day, that range is specified in terms of  
21 Trazodone the drug, right, not paroxetine?

22 A That's correct. To get to paroxetine you use that  
23 conversion factor.

24 Q And that would be the conversion factor you have on  
25 slide 30?

1 A There is a table there, yes.

2 Q Okay.

3 So go back to 31, please.

4 And the calculation that you have here, it's also  
5 dependent on making an assumption of the weight to use for  
6 the woman who's going to receive this dose of Trazodone.  
7 Right?

8 A That's correct.

9 Q And you chose 70 kilograms for your calculation?

10 A That's correct.

11 Q And you agree, that actually if you were to use a  
12 different weight that would impact the overall range that  
13 you come up with for the paroxetine amount down at the  
14 bottom, where you say 0.21 to 8.4. Right?

15 A It definitely effect the range, if you realize that the  
16 bottom of the range is so small that it's always going to be  
17 around -- around one, and the top numbers are what's going  
18 to change the most. But it will change, the range will  
19 change.

20 Q So certainly, if you were to use instead an assumption  
21 of 65 kilograms for the weight of the woman to receive the  
22 dose, that would lower that upper end of the range of 8.4.  
23 Right?

24 A Right.

25 But then it would show that it's useful down to,

1 let's say point -- you know, .3 or something.

2 Q But no longer useful as high as 8.4. Right?

3 A Well, if it's -- if it's useful down to -- down to .3,  
4 then I think it's reasonable to make an assumption that it's  
5 effective above that dose as well.

6 Q So, in your opinion Coelingh's teaching more than just  
7 the particular ranges that are here on your slide 31?

8 A I'm not sure I understand what your question is.

9 Q My question is, if you use a lower amount for the weight  
10 of the woman, lower than 70, that upper end of 8.4, it's not  
11 going to be 8.4 anymore. Right? It's going to be lower.

12 A That's correct.

13 Q So is it your opinion that -- that's fine.

14 But we agree that if you use a lower weight for the  
15 woman to receive the dose, that upper end that's disclosed  
16 by Coelingh is going to decrease as well. Right?

17 A Correct.

18 You could use the Claim 2 dosing that doesn't  
19 include the weights, and then you have a little bit broader  
20 dosing range.

21 Q But for the dosage range that you, you know, that you  
22 had in your report, that you based your opinions on, it is  
23 dependent on that -- on that weight of the woman who's  
24 receiving the dose. Right?

25 A It is.

1 Q It's subject to that variability and that assumption  
2 that you had to apply the 70 kilogram woman being the  
3 appropriate number to apply?

4 A That's the assumption.

5 Q Chris, could we turn back to slide 30, please, from Dr.  
6 Locker's demonstratives.

7 You said that Trazodone conversion factor is set  
8 forth in the Coelingh application. Right?

9 A Yes.

10 Q And you don't know how these conversion factors were  
11 determined. Right?

12 A No, I do not.

13 Q You don't know why Citalopram has a conversion factor of  
14 .15 just like paroxetine. Right?

15 A That's correct.

16 Q You don't know why Fluoxetine was also given a  
17 conversion factor of 0.15. Right?

18 A That's correct.

19 Q And there's no data in the patent explaining or  
20 supporting those conversion factors. Right?

21 A That's correct.

22 Q In fact, you just have no idea where those conversion  
23 factors came from?

24 A It's not clearly stated in the paper.

25 Q It's not stated at all. Right?

1 A That's correct.

2 Q Let's go back to the example. This would be the last  
3 page of PTX 982, I believe, or second to last page.

4 Actually, no, at page 12. And let's pull up the example,  
5 the last, like the bottom half of it.

6 So Coelingh's example predicts that 20 milligrams  
7 of Fluoxetine alone would be effective to treat hot flashes.  
8 Right?

9 A That's correct.

10 Q And Coelingh's example also predicts that five  
11 milligrams of Fluoxetine plus 50 milligrams of Vitamin B 6  
12 will be effective to treat hot flashes. Right?

13 A Yes, it is.

14 Q If Fluoxetine were shown to be effective to treat hot  
15 flashes at a dose of five milligrams per day, as you suggest  
16 by this example, would that lead you to expect that  
17 paroxetine would also be useful to treat hot flashes at a  
18 dose of five milligrams per day?

19 A Again, I would -- this is just an example. I would go  
20 ahead and use the conversion factor like we did. And then  
21 according to what we did, you know, the calculations we  
22 used, then it would be -- again, I would go back to that  
23 range.

24 Q Okay.

25 And this example is telling you that five

1 milligrams of Fluoxetine is going to work. Right?

2 A That's correct.

3 I believe five milligrams was also within the  
4 ranges of both of the examples that we used.

5 Q And the conversion factor for Fluoxetine is -- the  
6 conversion factor for Fluoxetine and paroxetine is the same.  
7 Right?

8 A That's correct.

9 Q So in your reading then, if Fluoxetine were to be  
10 effective, then based on that same conversion factor and  
11 calculation, then you would expect paroxetine to be useful  
12 as well for treating VMS at a dose of five milligrams.  
13 Right?

14 A That's inclusive of that range, so yes, I would believe  
15 that.

16 Q And in your opinion, a person of skill in the art would  
17 simply accept that conversion factor of Coelingh without any  
18 data supporting it?

19 A I have no reason not to believe this.

20 MS. PETERSON: Your Honor, I don't have any other  
21 questions for Dr. Locker at this point.

22 I will note for the record, however, that the  
23 defendants have indicated that they intend to recall Dr.  
24 Locker to testify later in the week on issues of secondary  
25 considerations. And well, of course we don't know the full

1 disclosed the use of SSRIs, specifically paroxetine, at the  
2 dosage amount of 10 milligrams per day, that based on that  
3 alone in the context of the patent without the benefit of the  
4 later Phase II data, that it would be reasonable to conclude  
5 that 7.5 milligrams per day of paroxetine would work?

6 A It seems like you're asking me now an obviousness question,  
7 because it's outside the full scope of the patent, including  
8 the issues that were disclosed to the Patent Office in the  
9 Lippman Declaration.

10 Could you clarify from what point of view I'm supposed  
11 to assess your question?

12 Q Doctor, is it reasonable to conclude that 7.5 milligrams  
13 per day of paroxetine would work to treat hot flashes based on  
14 the prior art without the benefit of the Phase II data?

15 A Without the benefit of the Phase II data, I think you'd  
16 have to test it. But that's, in fact, what was done.

17 MR. CUNNING: Can you turn to page 170 of Dr. Simon's  
18 deposition transcript, starting at line 14.

19 You have to take this through the end of that page and  
20 go to the next page.

21 Q And, Doctor, you have the deposition transcript again there  
22 if you want to follow along.

23 We were discussing at the time your expert report and  
24 you wrote: (Reading) The credibility of the utility is  
25 supported by the patents and publications discussed and

1 A If you apply those numbers, you can force a range as you  
2 suggested. I think it's rather creative, but, yes.

3 Q In your expert report you had charged that Dr. Locker  
4 selectively picked a 70 kilogram weight amount in order to  
5 encompass the seven-and-a-half milligram dosage amount?

6 A I just used the word "forced example."

7 Q If I understood you correctly on direct, you admit that 70  
8 kilograms is a reasonable estimate for women in the menopausal  
9 age range?

10 A It's getting pretty up there but, yes. In the 1960s it was  
11 the average weight of a male.

12 MR. CUNNING: Can we pull up Defendants' Trial Exhibit  
13 361, please.

14 MS. PETERSON: Your Honor, we object to Defendants'  
15 Exhibit 361, it's not on their exhibit list.

16 MR. CUNNING: It's for impeachment, your Honor.

17 THE COURT: What was the last question?  
18 How do you intend to use this?

19 MR. CUNNING: I'm sorry?

20 THE COURT: How do you intend to use it?

21 MR. CUNNING: This exhibit is weight and other  
22 biometric data from the CDC in the 2007-2010 timeframe, and it  
23 lists the percentile weights for women in various age groups.

24 THE COURT: Go ahead. I'll weigh it accordingly.  
25 Go ahead.

1 BY MR. CUNNING:

2 Q If you could turn to page 7 of the document, please.

3 MR. CUNNING: Could we just pull up the top section.

4 THE WITNESS: Could you make it a little larger,  
5 please?

6 MR. CUNNING: Right there. Correct.

7 Q So, here it lists a range of ages for all racial and ethnic  
8 groups in the United States for women age 20 and over.  
9 Correct?

10 A That's correct.

11 Q And if we look at the 50th percentile for women in the age  
12 range of 50 to 59, the weight listed is 73.2 kilograms.  
13 Correct?

14 A That's correct.

15 Q I believe you testified that the average age of onset for  
16 menopause is 51?

17 A I did.

18 MR. CUNNING: You can take that down.

19 Can we bring up Plaintiff's Demonstrative Exhibit 536,  
20 please.

21 Q Now, here you say that Coelingh only mentions paroxetine as  
22 one of many others. Correct?

23 A Correct.

24 Q And you've highlighted a list of different SRIs that are  
25 mentioned in the Coelingh reference?

1 wanted me to clarify a question, you should ask me and I would  
2 be happy to do so.

3 A You did ask me -- you did suggest that if I wasn't clear on  
4 something, that I ask you.

5 Q On page 167 -- I'm sorry -- 176 at line 8, going down to  
6 line 12:

7 (Reading) Do you have an expectation one way or the  
8 other, without testing the 9 milligram dosage amount, as to  
9 whether it would be effective?

10 You answered: It might be. I don't know.

11 Correct?

12 A That's what the words on the page say.

13 Q Sir, if I asked that same question for every dosage amount  
14 of paroxetine mesylate listed in example 1 below 8, your answer  
15 is the same. Correct?

16 A Are we asking the hypothetical from before the time of the  
17 patent, before there was any clinical data? What are we asking  
18 here?

19 Q At the same --

20 A You're asking me, again -- are you asking me what I said in  
21 my deposition, or are you asking me again?

22 Q Well, right now I'm asking you now: Considering the '663  
23 Patent from the perspective of one of skill in the art in  
24 August of 2006, without the benefit of the Phase II clinical  
25 trial data, do you have any expectation one way or the other

1 whether dosages less than 8 milligrams per day would be  
2 effective to treat hot flashes?

3 A I wouldn't know. As a scientist, I'd require experimental  
4 testing.

5 MR. CUNNING: Can we pull up Plaintiff's Demonstrative  
6 514, please.

7 Q And this is a time line you prepared showing --

8 MR. CUNNING: You know what, do we have the corrected,  
9 Dr. Simon's corrected version?

10 Q If not, I don't want to mislead you, and for whatever  
11 reason on the printout we don't have the WHI study, but that  
12 goes to 2002. Correct?

13 A It does.

14 Q There we go.

15 A Perfect.

16 Q In your opinion, there was a long-felt need in the medical  
17 community for a safe and effective non-hormonal treatment  
18 option for hot flashes?

19 A Correct.

20 Q And that need was highlighted by the WHI study that was  
21 published in 2002?

22 A No, the need had been there for a long time but it was  
23 further exemplified by the WHI study when scores of women,  
24 several million in total, discontinued their hormone therapy  
25 for fear of the adverse events pointed out in the WHI 2002

# EXHIBIT 40

15992 U.S. PTO

Atty. Dkt. No. 091856-0114



120108

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Richards, P.A.T.  
  
Title: METHOD OF TREATING  
THERMOREGULATORY  
DISFUNCTION WITH  
PAROXETINE  
  
Appl. No.: CON of 11/499,586  
  
Filing Date: December 1, 2008  
  
Examiner: Unassigned  
  
Art Unit: Unassigned

**CONTINUING PATENT APPLICATION**  
**TRANSMITTAL LETTER**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Transmitted herewith for filing under 37 C.F.R. § 1.53(b) is a:

☒ Continuation    ☐ Division    ☐ Continuation-In-Part (CIP)

of the above-identified copending prior application in which no patenting, abandonment, or termination of proceedings has occurred. Priority to the above-identified prior application is hereby claimed under 35 U.S.C. § 120 for this continuing application. The entire disclosure of the above-identified prior application is considered as being part of the disclosure of the accompanying continuing application and is hereby incorporated by reference therein.

☐ Applicant claims small entity status under 37 CFR 1.27.

Enclosed are:

☒ Description, Claim(s), and Abstract (15 pages).  
☒ Declaration and Power of Attorney (3 pages).

Atty. Dkt. No. 091856-0114

- ☒ Statement Under 37 CFR 3.73(b) (1 page, copy from parent application)
- ☒ Power of Attorney to Prosecute Applications Before USPTO  
(1 page, copy from parent application)
- ☒ Information Disclosure Statement (2 pages).
- ☒ Form PTO-SB/08 (3 pages).
- ☒ Application Data Sheet (37 CFR 1.76).

The filing fee is calculated below:

	Number Filed	Included in Basic Fee	Extra	Rate	Fee Totals
Basic Filing Fee				\$330.00 =	\$330.00
Search Fee				\$540.00	\$540.00
Examination Fee				\$220.00	\$220.00
Size Fee	12	- 100	= 0 x	\$270.00	\$0.00
Total	12	- 20	= 0 x	\$52.00 =	\$0.00
Claims:					
Independents	1	- 3	= 0 x	\$220.00 =	\$0.00
:					
If any Multiple Dependent Claim(s) present:			+	\$390.00 =	\$0.00
Surcharge under 37 CFR 1.16(e) for late filing of Executed Declaration or late payment of filing fee			+	\$130.00 =	\$0.00
				SUBTOTAL: =	\$1090.00
<input type="checkbox"/> Small Entity Fees Apply (subtract ½ of above):				=	
Basic Filing Fee Reduction for Filing via EFS-Web					\$0.00
				TOTAL FILING FEE: =	1090.00
Assignment Recordation Fee:			+	\$40.00 =	\$0.00
Processing Fee under 37 CFR 1.17(i) for Late Filing of English Translation of Application:			+	\$130.00 =	\$0.00
TOTAL FEE				=	1090.00

Atty. Dkt. No. 091856-0114

The required filing fees are not enclosed but will be submitted in response to the Notice to File Missing Parts of Application.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date December 1, 2008

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By Courtenay C. Brinckerhoff

Courtenay C. Brinckerhoff  
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Registration No. 37,288



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant: Patricia Allison Tewes Richards  
Title: Method of Treating Thermoregulatory Dysfunction with Paroxetine  
Appl. No.: 12/292,960  
Filing Date: 12/01/2008  
Examiner: Shobha Kantamneni  
Art Unit: 1627  
Confirmation Number: 9552

BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Under the provisions of 37 C.F.R. § 41.37, this Appeal Brief is being filed together with a credit card payment form in the amount of \$540.00, covering the appeal fee set forth in 37 C.F.R. 41.20(b)(2). If this fee is deemed to be insufficient, authorization is hereby given to charge any deficiency (or credit any balance) to the undersigned deposit account 19-0741.

## TABLE OF CONTENTS

<b>I.</b>	<b>REAL PARTY IN INTEREST .....</b>	<b>5</b>
<b>II.</b>	<b>RELATED APPEALS AND INTERFERENCES .....</b>	<b>6</b>
<b>III.</b>	<b>STATUS OF CLAIMS .....</b>	<b>7</b>
<b>IV.</b>	<b>STATUS OF AMENDMENTS .....</b>	<b>8</b>
<b>V.</b>	<b>SUMMARY OF CLAIMED SUBJECT MATTER.....</b>	<b>9</b>
<b>VI.</b>	<b>GROUND OF REJECTION TO BE REVIEWED ON APPEAL .....</b>	<b>10</b>
<b>VII.</b>	<b>ARGUMENT .....</b>	<b>11</b>
<b>A.</b>	<b>THE METHODS OF THE INDEPENDENT CLAIMS ARE NOT OBVIOUS .....</b>	<b>11</b>
1.	<i>Combining Stearns (2000), Jenkins (U.S. 6,369,051), and Gould (1986) Does Not Make Out A Prima Facie Case Of Obviousness of Claims 13, 15 and 22.....</i>	<i>12</i>
a)	The rejection overstates the teachings of Stearns (2000).....	12
b)	The rejection misapplies the teachings of Jenkins .....	14
c)	Gould does not provide any reasonable expectation of success .....	16
d)	An expectation of reduced side effects does not provide any reasonable expectation of therapeutic efficacy .....	16
2.	<i>Combining Stearns (2005) and Gould (1986) Does Not Make Out A Prima Facie Case Of Obviousness of Claims 13, 15 and 22 .....</i>	<i>16</i>
a)	The rejection overstates the teachings of Stearns (2005).....	17
b)	Gould does not provide any reasonable expectation of success .....	18
c)	An expectation of reduced side effects does not provide any reasonable expectation of therapeutic efficacy .....	18
3.	<i>The Lippman Declaration Provides Evidence Of Non-Obviousness ...</i>	<i>19</i>
4.	<i>In re Boesch does not control the instant obviousness inquiry.....</i>	<i>23</i>

<b>B.</b>	<b>THE DEPENDENT CLAIMS ARE NOT OBVIOUS</b> .....	24
1.	<i>Combining Stearns (2005), Gould, and Barnes (U.S. 4,721,723) Does Not Make Out A Prima Facie Case Of Obviousness of Claim 20</i> .....	24
2.	<i>Combining Stearns (2005), Gould, and Murthy (U.S. 6,436,956) Does Not Make Out A Prima Facie Case Of Obviousness of Claim 21</i> .....	25
<b>C.</b>	<b>CONCLUSION</b> .....	26
<b>VIII.</b>	<b>CLAIMS APPENDIX</b> .....	27
<b>IX.</b>	<b>EVIDENCE APPENDIX</b> .....	28
<b>X.</b>	<b>RELATED PROCEEDINGS APPENDIX</b> .....	29

**TABLE OF AUTHORITIES****CASES**

<i>KSR International Co. v. Teleflex, Inc.</i> , 127 S. Ct. 1727 (U.S. 2007) .....	11, 24, 25
<i>In re Boesch</i> , 205 USPQ 215 (CCPA 1980) .....	23
<i>Eli Lilly &amp; Co. v. Teva Pharm. USA, Inc.</i> , 57 F. Supp 2d 967 (S. D. In. 2009); aff'd 619 F.3d 1329, 96 USPQ.2d 1375 (Fed. Cir. 2010) .....	11, 12, 16, 19

**FEDERAL STATUTES**

35 U.S.C. § 103 .....	11, 24
-----------------------	--------

**PATENT OFFICE GUIDANCE DOCUMENTS**

MPEP § 2141 .....	24, 25
MPEP § 2143.02 .....	11, 16, 19

**I. REAL PARTY IN INTEREST**

The real party in interest is Noven Therapeutics, LLC.

**II. RELATED APPEALS AND INTERFERENCES**

No prior or pending appeals, judicial proceedings or interferences are known to the Appellant which may be related to, directly affect, be directly affected by, or have a bearing on the Board's decision in this appeal.

**III. STATUS OF CLAIMS**

Claims 1-12, 14, and 16-19 are canceled.

Claims 13, 15, and 20-22 are pending, rejected, and on appeal.

**IV. STATUS OF AMENDMENTS**

The after-final amendments submitted with the response filed February 8, 2011, have been entered, as indicated in the Advisory Action mailed May 31, 2011.

## V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter relates to methods for treating a patient suffering from a thermoregulatory dysfunction associated with menopause that comprises administering paroxetine mesylate in an amount of 7.5 mg/day, based on the paroxetine moiety. As discussed in paragraph [0005] at page 2 of the specification, the claimed methods meet a need in the art for an effective, non-hormonal therapy for thermoregulatory dysfunction (e.g., hot flushes and hot flashes). Another contribution of the claimed methods is the ability to use a dose of paroxetine that is below the dose typically used to treat depression. See, e.g., paragraph [0009], at pages 4-5. This avoids the effects (including side effects and other risks) associated with higher doses of selective serotonin reuptake inhibitors (SSRIs) such as paroxetine. The two independent claims on appeal are claim 13 and claim 22:

Claim 13 is directed to a method for treating a patient suffering from a thermoregulatory dysfunction associated with menopause (**paragraph [0020], page 8, lines 21-23 and page 9, lines 6-8**) comprising administering paroxetine mesylate (**paragraph [0018], page 7, line 21 and page 8, line 3**) to said patient in an amount, based on the paroxetine moiety, of 7.5 mg/day (**paragraph [0019], page 8, lines 12 and 18**).

Claim 22 is directed to a method for treating a patient suffering from a thermoregulatory dysfunction associated with menopause (**paragraph [0020], page 8, lines 21-23 and page 9, lines 6-8**) comprising administering paroxetine (**paragraph [0017], page 7, lines 10-12**) to said patient, wherein said paroxetine is in the form of a pharmaceutically acceptable mesylate salt (**paragraph [0018], page 7, line 21 and page 8, line 3**), in amorphous or crystalline form, and mixtures thereof (**paragraph [0017], page 7, lines 10-12**), wherein said paroxetine mesylate is administered in an amount, based on the paroxetine moiety, of 7.5 mg/day (**paragraph [0019], page 8, lines 12 and 18**).

The Rule 132 Declaration of Dr. Lippman submitted with the response filed September 21, 2010, presents the results of a human clinical trial that demonstrated the surprising and unexpected efficacy the claimed methods, showing that “paroxetine mesylate at 7.5 mg/day (based on the paroxetine moiety) was safe, well tolerated and more effective than placebo in the treatment of vasomotor symptoms (thermoregulatory dysfunction) associated with menopause.” Lippman Declaration, ¶ 13.

**VI. GROUND OF REJECTION TO BE REVIEWED ON APPEAL**

1. The rejection of claims 13, 15 and 22 under 35 USC § 103 for alleged obviousness in view of Stearns (2000), Jenkins (U.S. 6,369,051) and Gould (1986).<sup>1</sup>
2. The rejection of claims 13, 15 and 22 under 35 USC § 103 for alleged obviousness in view of Stearns (2005) and Gould (1986).
3. The rejection of claim 20 under 35 USC § 103 for alleged obviousness in view of Stearns (2005), Gould (1986) and Barnes (U.S. 4,721,723).
4. The rejection of claim 21 under 35 USC § 103 for alleged obviousness in view of Stearns (2005), Gould (1986) and Murthy (U.S. 6,436,956).<sup>2</sup>

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<sup>1</sup> The Advisory Action mailed May 31, 2011 states that the “amended claims remain rejected over the prior art employed in the final rejection,” but the rejections listed in the Advisory Action do not include a citation of Jenkins. However, because the Advisory Action discusses the combination of Stearns (2000) and Jenkins, Appellant believes that the Examiner still intends to apply Jenkins in combination with Stearns (2000) and Gould against claims 13, 15 and 22. Appellant respectfully urges clarification in the next Office communication or in the Examiner’s Answer.

<sup>2</sup> The Advisory Action indicates that claims 21 is rejected over the combination of Stearns (2005), Gould, and “Barnes (US 6,436,956)”. However, the cited Barnes patent is U.S. 4,721,723, as applied against claim 20. On the other hand, U.S. 6,436,956 was issued to Murthy et al.. Thus, Appellant believes that the Examiner intends to apply “Murthy (US 6,436,956)” in combination with Stearns (2005) and Gould against claim 21. Appellant respectfully urges clarification in the next Office communication or in the Examiner’s Answer.

## VII. ARGUMENT

### A. THE METHODS OF THE INDEPENDENT CLAIMS ARE NOT OBVIOUS

The rejections on appeal are founded on the assertion that “one of ordinary skill would have been motivated to determine the effective amounts of paroxetine,” or “would have been motivated to administer lower doses of paroxetine.” *See, e.g.*, Final Office Action, pages 4 and 7. In essence, the rejections are based on the premise that it would have been “obvious to try” the dose of paroxetine mesylate recited in the instant claims. However, as discussed in *KSR International Co. v. Teleflex, Inc.*, “obvious to try” only may be invoked to establish obviousness when “there are a finite number of identified, predictable solutions.” *KSR*, 127 S. Ct. 1727, 1742 (U.S. 2007) (emphasis added). Indeed, as set forth in MPEP § 2143.02, an obviousness rejection requires “at least some degree of predictability.”

A similar issue was raised in *Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 57 F. Supp.2d 967 (S. D. In. 2009); *aff’d* 619 F.3d 1329, 96 USPQ.2d 1375 (Fed. Cir. 2010). One of the patents at issue was directed to a method of preventing post-menopausal osteoporosis using a raloxifene hydrochloride salt at a dose of 60 mg/day. *Eli Lilly*, 57 F. Supp.2d at 976. The prior art included a patent that disclosed the use of raloxifene at doses of from 0.05 to 50 mg/kg/day. *Id.* at 986. Teva argued that the claims were invalid as obvious “because [the inventor] merely conducted routine testing to reach the 60 mg/day dose.” *Id.* at 1014.

The court acknowledge that “conducting clinical trials to test for an optimal dose . . . is generally a routine process,” but noted that “it is also well established that ‘patentability shall not be negated by the manner in which the invention was made,’” citing 35 USC § 103. *Id.* at 1015. The court found that because “a person of ordinary skill in the art would not have had a reasonable likelihood of success in using a low dose of raloxifene to treat or prevent postmenopausal osteoporosis,” the claims were not obvious. Although the court cited some prior art discussions of “bioavailability problems,” the foundational factual finding that at the time of the invention it was believed “that a large dose of the drug would be necessary to be effective” pertains to the instantly claimed methods as well, as discussed below with reference to the evidence of record.

On appeal, the Federal Circuit affirmed the district court, including the finding that “a person of ordinary skill in the art would not have had a reasonable expectation of success in using such a low dose of raloxifene to treat postmenopausal osteoporosis.” *Eli Lilly*, 619 F.3d at 1341-42.

As noted below, the prior art of record at best indicates that a dose of paroxetine 33% **higher** than the recited dose may be effective against hot flashes, and that even higher doses may be required for many patients. The uncontroverted evidence of record (including the Rule 132 Declaration of Dr. Lippman) shows that the ability of paroxetine mesylate to treat thermoregulatory dysfunction associated with menopause at doses of 7.5 mg/day was not predictable, and could not have been expected from the cited prior art references.

Thus, the pending §103 rejections are improper and so should be reversed.

1. *Combining Stearns (2000), Jenkins (U.S. 6,369,051), and Gould (1986) Does Not Make Out A Prima Facie Case Of Obviousness of Claims 13, 15 and 22*

As reflected in the language of claim 13, independent claims 13 and 22 recite methods for treating a patient suffering from a thermoregulatory dysfunction associated with menopause comprising administering paroxetine mesylate in an amount, based on the paroxetine moiety, of 7.5 mg/day. (Claim 22 further recites that the paroxetine mesylate may be in amorphous or crystalline form, or mixtures thereof.) The combination of Stearns (2000), Jenkins, and Gould does not teach or suggest such methods or otherwise indicate that the recited amount of paroxetine is effective to treat thermoregulatory dysfunction associated with menopause, and fails to provide any reasonable expectation of success in that regard. Accordingly, Stearns (2000), Jenkins, and Gould do not render obvious the claimed methods, and this §103 rejection should be reversed.

a) The rejection overstates the teachings of Stearns (2000)

The obviousness rejection overstates the teachings of Stearns (2000), as Stearns (2000) does not teach, suggest, or otherwise indicate that a dose of paroxetine lower than 10 mg/day is effective against thermoregulatory dysfunction associated with menopause.

Stearns (2000) reports the results of a pilot clinical trial in 30 patients that assessed the efficacy of paroxetine hydrochloride against hot flashes in breast cancer survivors. *See, e.g.,* Stearns (2000), page 17, *Summary*. In the study, patients were administered paroxetine hydrochloride at 10 mg/day for 7 days “to assess side effects” and then were administered paroxetine hydrochloride at 20 mg/day for 4 weeks to assess efficacy. *See, e.g.,* Stearns (2000), page 18, col 2., *Study Design*. Out of the 27 patients who completed the trial, two decreased their dose to 10 mg/day due to the side effect of somnolence experienced at the 20 mg/day dose. Stearns (2000), page 19, col 2., *Safety and tolerability*. The reference does not indicate when these patients adjusted their dose or reveal whether these patients were among those who reported a reduction in hot flashes.

The Examiner has acknowledged that Stearns (2000) does not teach a dose of paroxetine of 7.5 mg/day. *See, e.g.,* final Office Action, page 3. Nevertheless, the Examiner asserts that Stearns supports the obviousness rejection because Stearns “teaches that the dosage can be varied” and that “lower dose have [sic] fewer side effects.” *See, e.g.,* May 31, 2011 Advisory Action. This characterization of Stearns (2000) reads too much into the reference. There is simply no teaching or suggestion in Stearns (2000) to use a dose of paroxetine lower than 10 mg/day.

On dosing, Stearns (2000) states at page 21, col. 1:

This pilot trial cannot answer questions related to the optimal dose of treatment. ... It is therefore possible that a dose of paroxetine of 10 mg daily might be sufficient in alleviating hot flashes. Also, it is possible that women who did not respond to the standard antidepressant dose of 20 mg might benefit from an increased paroxetine dose.

Thus, at best, Stearns (2000) indicates that a paroxetine dose of 10 mg/day *might* be effective. It certainly does not suggest that a dose **25% lower** than 10 mg/day (7.5 mg/day) would be effective, let alone provide any reasonable expectation of success in that regard.

b) The rejection misapplies the teachings of Jenkins

While the rejection relies on Jenkins to suggest a lower dose of paroxetine, combining Jenkins with Stearns (2000) does not suggest the claimed methods or provide any reasonable expectation of success.

Jenkins is directed to therapeutic methods using certain substituted indole compounds in combination with an SSRI, including paroxetine and others. According to Jenkins, its combination therapy is useful against a host of conditions that includes hot flushes.

The Office Action cites the following sentence of Jenkins as teaching a dose of paroxetine that encompasses the recited dose:

Effective administration of these compounds may be given at an effective dose of from about 0.1 mg/day to about 500 mg/day.

Jenkins, col. 15, lines 57-59.

While page 4, paragraph [0008] of Appellant's specification also refers to this passage of Jenkins as "mention[ing] a broad dosage range for the SSRI component of the SSRI/estrogenic substance combinations," upon further review of Jenkins as a whole, Appellant does not believe that this passage unambiguously relates to the SSRI component of Jenkins' combination therapy, as discussed in the Responses filed September 22, 2010, and February 8, 2011.

As explained in these Responses, this passage of Jenkins is sandwiched between paragraphs that discuss Jenkins' substituted indole component (only) or that generally discuss both components. The very next few paragraphs set forth more specific dosages for specific substituted indoles (the non-SSRI component of Jenkins' therapy). Thus, the identity of "these compounds" in the cited passage is ambiguous. Moreover, even if the cited passage of Jenkins is understood to apply to SSRIs generally, it would not be understood to apply to paroxetine specifically, particularly when Jenkins provides more specific teachings on paroxetine doses.

At column 16, line 48, Jenkins expressly addresses the dosage of the SSRI component of its combination therapy:

The SSRI compounds of these methods may be administered in regimens and at dosages known in the art.

When discussing paroxetine in particular in that same paragraph, Jenkins states:

Paroxetine hydrochloride, offered by SmithKline Beecham, Inc. under the Paxil® name, has a recommended daily dosage of from **20 to 50 mg**.

Jenkins, col. 16, lines 58-60 (emphasis added).

Thus, the skilled artisan reading Jenkins as a whole would understand it to teach a dose of paroxetine of 20-50 mg/day, not a dose lower than the 10 mg/day used in Stearns (2000), and certainly not a dose as low as the 7.5 mg/day recited in the instant claims.

Moreover, Jenkins does not correlate the broad dosage ranges set forth in column 15 with any of the specific conditions its combination therapies are said to be useful against. As set forth at col. 1, lines 9-17, Jenkins teaches that its combination of substituted indoles and SSRI agents can be used to treat a wide variety of conditions, including:

depression, anxiety, generalized anxiety disorder (GAD), hot flush, post partum depression, premenstrual syndrome, obesity, obsessive compulsive disorder, post-traumatic stress disorder, social phobia, disruptive behavior disorders, impulse control disorders, borderline personality disorder, chronic fatigue disorder, premature ejaculation, pain, attention deficit disorders, with and without hyperactivity, Gilles de la Tourette syndrome, bulimia nervosa, or Shy Drager Syndrome.

Jenkins does not provide any teachings of specific doses that are effective against one or more of these conditions. The skilled artisan reading Jenkins certainly would not understand the passage at column 15 to teach or suggest that *every* dose of *every* SSRI within the range of 0.1 mg/day to 500 mg/day is useful against *every* condition mentioned in Jenkin, let alone that a dose of 7.5 mg/day paroxetine is effective against hot flashes.

Thus, there is no teaching in Jenkins that could provide any reasonable expectation of success that a paroxetine dose lower than the 10 mg/day used by Stearns (2000) is useful against hot flashes.

c) Gould does not provide any reasonable expectation of success

Gould was cited for teaching different salts for basic drugs, including mesylate. It is not directed to paroxetine in particular, or to any specific therapeutic methods. Thus, the combination of Stearns (2000), Jenkins and Gould does not teach or suggest the recited methods, or provide any reasonable expectation of success that a 7.5 mg/day dose of paroxetine would be effective to treat thermoregulatory dysfunction associated with menopause.

d) An expectation of reduced side effects does not provide any reasonable expectation of therapeutic efficacy

As reflected in the Advisory Action mailed May 31, 2011, at page 2, 4<sup>th</sup> paragraph, the rejection is based on the assertion that one of ordinary skill in the art would have had a “reasonable expectation of success of treating hot flashes with fewer side effects because Stearns et al. teach that lower doses of paroxetine have fewer side effects.” This misses the point of unpredictability. While Stearns (2000) may provide a reasonable expectation that a lower dose of paroxetine would have fewer *side effects*, it provides no expectation whatsoever that a dose of 7.5 mg/day would exhibit a *therapeutic effect* in the treatment of thermoregulatory dysfunction associated with menopause.

Without a reasonable expectation of success, the § 103 rejection is improper and should be reversed. *See Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 57 F. Supp.2d 967 (S. D. In. 2009); *aff’d* 619 F.3d 1329, 96 USPQ.2d 1375 (Fed. Cir. 2010); MPEP § 2143.02.

2. *Combining Stearns (2005) and Gould (1986) Does Not Make Out A Prima Facie Case Of Obviousness of Claims 13, 15 and 22*

The teachings of Stearns (2005) are similar to those of Stearns (2000) in that Stearns (2005) does not teach or suggest that a dose of paroxetine lower than 10 mg/day is effective against hot flashes. Thus, the combination of Stearns (2005) and Gould does not

teach or suggest the recited methods or otherwise indicate that the recited amount of paroxetine is effective to treat thermoregulatory dysfunction associated with menopause, and fails to provide any reasonable expectation of success in that regard. Accordingly, Stearns (2005) and Gould do not render obvious the claimed methods, and this §103 rejection should be reversed.

a) The rejection overstates the teachings of Stearns (2005)

The obviousness rejection overstates the teachings of Stearns (2005), as Stearns does not teach, suggest, or otherwise indicate that a dose of paroxetine lower than 10 mg/day is effective against thermoregulatory dysfunction associated with menopause.

Stearns (2005) reports a clinical trial designed to investigate the efficacy of paroxetine at 10 mg/day or 20 mg/day in reducing hot flashes, using an immediate release formulation of paroxetine hydrochloride. *See, e.g.*, Stearns (2005), Abstract. The study included 151 patients who were randomly assigned to receive 10 mg/day or 20 mg/day. *See, e.g.*, Stearns (2005), Abstract. The patients also were followed over 4 weeks of placebo administration, either before or after the paroxetine administration. *See, e.g.*, Stearns (2005), Abstract. Stearns (2005) reports that the 10 mg dose reduced hot flash frequency by 40.6%, while the 20 mg dose reduced hot flash frequency by 51.7%. *See, e.g.*, Stearns (2005), Abstract. The authors concluded that “[e]fficacy was similar between the two doses, but women were less likely to discontinue low-dose paroxetine.” *See, e.g.*, Stearns (2005), Abstract.

The Examiner has acknowledged that Stearns (2005) does not teach a dose of paroxetine of 7.5 mg/day. *See, e.g.*, final Office Action, page 6. Nevertheless, the Examiner asserts that Stearns supports the obviousness rejection because Stearns (2005) mentions a “lower dose” of paroxetine. To the extent that the Examiner asserts that Stearns (2005) refers to a dose **lower** than the lowest dose (10 mg/day) used in its clinical trial, the Examiner is incorrect.

The lowest dose of paroxetine mentioned in Stearns (2005) is 10 mg/day. Indeed, Stearns (2005) refers to the 10 mg/day dose as a “low dose.” For example, at page 6920,

col. 1, 1<sup>st</sup> full paragraph, Stearns (2005) states that an objective of the clinical trial was “to compare the effectiveness of the standard starting dose of paroxetine for depression . . . (20 mg) and *low-dose (10 mg)* for the treatment of hot flashes” (emphasis added).

Moreover, Stearns (2005) concludes:

We recommend prescribing *low-dose of paroxetine (10 mg)* to women who desire a nonhormonal pharmacologic treatment for their hot flashes.

Stearns (2005), page 6929, col. 2 (emphasis added). Far from teaching or suggesting the use of a lower dose, Stearns (2005) notes that they “have not studied escalating doses of paroxetine and cannot recommend an increase in the dose more than 20 mg/day.” Stearns (2005), page 6928, col. 2, last paragraph. If anything, this passage of Stearns (2005) suggests that *higher* doses should be studied.

Thus, contrary to the implications in the Office Actions, there is no teaching or suggestion in Stearns (2005) to use a dose lower than the 10 mg “low dose” it tested, let alone to use a dose as low as the 7.5 mg/day dose recited in the instant claims, which is *25% lower* than Stearn’s “low” dose.

b) Gould does not provide any reasonable expectation of success

Gould was cited for teaching different salts for basic drugs, including mesylate. It is not directed to paroxetine in particular, or to any specific therapeutic methods. Accordingly, the combination of Stearns (2005) and Gould does not teach or suggest the recited methods, or provide any reasonable expectation of success that a 7.5 mg/day dose of paroxetine would be effective to treat thermoregulatory dysfunction associated with menopause.

c) An expectation of reduced side effects does not provide any reasonable expectation of therapeutic efficacy

As reflected in the final Office Action at page 7, 1<sup>st</sup> paragraph, the rejection is based on the assertion that one of ordinary skill in the art would have had a “reasonable expectation of success of treating hot flashes with fewer side effects” because Stearns (2005) teaches that “lower doses of paroxetine have fewer side effects.” As discussed above with reference to the rejection citing Stearns (2000), this statement misses the point

of unpredictability. While Stearns (2005) may provide a reasonable expectation that a lower dose of paroxetine would have fewer *side effects*, it provides no expectation whatsoever that a dose of 7.5 mg/day would exhibit a *therapeutic effect* in the treatment of thermoregulatory dysfunction associated with menopause.

Without a reasonable expectation of success, the § 103 rejection is improper and should be reversed. *See Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 57 F. Supp.2d 967 (S. D. In. 2009); *aff'd* 619 F.3d 1329, 96 USPQ.2d 1375 (Fed. Cir. 2010); MPEP § 2143.02.

3. *The Lippman Declaration Provides Evidence Of Non-Obviousness*

The Rule 132 Declaration of Dr. Lippman provides further evidence of non-obviousness by attesting to the unexpected results achieved by the claimed methods. Dr. Lippman is Executive Vice President - Clinical Development & Chief Medical Officer, at Noven Pharmaceuticals, Inc., which is affiliated with Noven Therapeutics, LLC, the assignee of the instant application. Dr. Lippman is an obstetrician-gynecologist certified by the American Board of Obstetrics and Gynecology, with nearly 20 years of clinical development and medical affairs experience in the pharmaceutical and device industries. Further credentials are set forth in ¶ 2 of his Declaration.

Dr. Lippman notes that “[c]ertain antidepressants/anti-anxiety agents, such as selective serotonin reuptake inhibitors (SSRIs), including paroxetine, have been proposed for use in non-hormonal therapies against hot flashes, but other effects of these drugs, including their antidepressive effects and associated side effects, raise serious concerns and make them contraindicated for many patients.” Lippman Declaration, ¶ 6.

Dr. Lippman presents the results of a human clinical trial that evaluated the subject matter of the instant claims, and that demonstrated the surprising and unexpected efficacy of paroxetine at 7.5 mg/day. Dr. Lippman reports that “[t]he clinical trial results as a whole showed that paroxetine mesylate at 7.5 mg/day (based on the paroxetine moiety) was safe, well tolerated and more effective than placebo in the treatment of vasomotor symptoms (thermoregulatory dysfunction) associated with menopause, particularly as

evidenced by decreases in the frequency and severity of moderate and severe hot flashes.” Lippman Declaration, ¶ 13.

Dr. Lippman emphasizes that “the present invention unexpectedly provides an effective therapy that is achieved at dosages of only 7.5 mg/day,” where “the lowest approved dosage for paroxetine is 10 mg/day.” Lippman Declaration, ¶ 6. “This reduced dose offers tremendous benefits to patients and their physicians, including lower risk and incidence of side effects, while still providing effective relief of symptoms of thermoregulatory dysfunction.” Lippman Declaration, ¶ 6. As Dr. Lippman explains, the discovery that paroxetine is effective against hot flashes at such a low dose could not have been predicted from the prior art.

Dr. Lippmann notes that “the lowest dose tested previously was 10 mg/day,” which is “33% greater than 7.5 mg/day”, and that higher doses such as “12.5 mg/day, 20 mg/day and 25 mg/day also have been tested for the treatment of hot flashes.” Lippman Declaration, ¶ 14. Dr. Lippman explains that, “[i]n view of these studies, reviewers suggest that patients initially be treated with doses of 10 or 12.5 mg/day, with the dose increased to 20 or 25 mg/day as needed to provide relief.” Lippman Declaration, ¶ 14. A similar conclusion is reached in Loprinzi, et. al. (2004) cited as item A51 in the IDS submitted December 1, 2008 and included in the Evidence Appendix.

As Dr. Lippman attests, “[i]n view of reports that higher doses are required to achieve efficacy in many patients, there was no clear expectation that a significantly lower dose could be used (25% less than 10 mg) and would prove effective, or that such a low dose would show success in terms of such significant end points as the frequency and severity of moderate and severe hot flashes.” Lippman Declaration, ¶ 14.

Thus, as Dr. Lippman attests, the clinical trial results “demonstrate an unexpected effect of the methods claimed in the Application,” and “show that the methods achieve an efficacy that could not have been predicted from the state of the art in August 2006.” Lippman Declaration, ¶ 15.

Dr. Lippman's testimony further undermines the obviousness rejections and demonstrates that the claimed methods achieve unexpected results. When the Lippman Declaration is given due consideration, it is clear that the obviousness rejections should be reversed.

In the final Office Action at page 9, the Examiner states that the Lippman Declaration is not persuasive because "Stearns et al. teach that lower dose of paroxetine have fewer side effects." Similarly, the Advisory Action mailed May 31, 2011 states that the Lippman Declaration is not persuasive because Stearns teaches that "lowering the dose of paroxetine . . . results in lower side effects." As discussed above, however, the possibility of reducing *side effects* at a lower dose does not answer the critical question of whether paroxetine will exhibit *therapeutic efficacy* at a lower dose. As shown by a review of the cited references, and as further discussed by Dr. Lippman, the understanding in the art was that patients could "initially be treated with doses of 10 or 12.5 mg/day, with the dose increased to 20 or 25 mg/day as needed to provide relief." Lippman Declaration, ¶ 14. There was no expectation that "a significantly lower dose could be used (25% less than 10 mg) and would prove effective." Lippman Declaration, ¶ 14. Thus, the stated rationale for maintaining the obviousness rejections is contradicted by the Declaration evidence provided by Dr. Lippman.

The final Office Action at page 9 also asserted that the Lippman Declaration was not commensurate with the scope of the claims, because it presented data obtained with paroxetine mesylate, while the claims pending at the time recited paroxetine generally. Without acquiescing on the merits, Appellant addressed that concern by amending the claims to recite paroxetine mesylate. Thus, the Lippman Declaration is fully commensurate with the scope of the claims on appeal.

The Advisory Action mailed May 31, 2011 turns this issue on its head, alleging for the first time on the written record<sup>3</sup> that the Lippman Declaration is not persuasive because it does not present evidence pertinent to the specific salt used in Stearns (2000) and Stearns (2005). In particular, the Advisory Action asserts that “different salts can have different efficacy, and thus the amounts needed for the same therapeutic effect for different salts can be different,” and criticizes the Lippman Declaration for not providing “any comparative data with the Stearns et al. hydrochloride salt of paroxetine at a dosage lower than 10 mg.” However, the Examiner has not cited any prior art, evidence or reasoning that could possibly shift the burden to Appellant on this point.

The record shows that Stearns (2000) and Stearns (2005) at best suggest that paroxetine can be effective against hot flashes at a dose of 10 mg/day, based on clinical trials that used paroxetine hydrochloride. There is no evidence of record that the skilled artisan would have expected paroxetine mesylate to be more potent against hot flashes than paroxetine hydrochloride. Thus, there is no basis for the implication that a skilled artisan might have expected Stearns’ reports of efficacy with 10 mg/day paroxetine hydrochloride to provide a reasonable expectation of success of being able to treat hot flashes with a 25% lower dose of paroxetine mesylate.

A rejection cannot be sustained on mere speculation, particularly where Appellant has provided evidence to the contrary. As summarized above, Dr. Lippman attested that the efficacy of the claimed methods was unexpected over the state of the art, including the use of 10 mg doses of paroxetine hydrochloride as reported by Stearns.

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<sup>3</sup> The Examiner noted that Stearns used a different salt during the Patent Office Interview conducted on April 6, 2011. As discussed during the Interview, Appellant is unable to obtain human clinical data using the paroxetine hydrochloride salt used by Stearns in order to support this patent application because of the very high costs, significant regulatory constraints, and considerable length of time required to design, implement and evaluate a human clinical trial. Moreover, Appellant has not argued patentability based on the specific salt used, but rather on the unexpected and unpredictable results achieved with the recited dose.

For at least the foregoing reasons, the pending obviousness rejections are contrary to the evidence of record and should be reversed.

4. *In re Boesch* does not control the instant obviousness inquiry

The final Office Action cited *In re Boesch*, 205 USPQ 215 (CCPA 1980), in support of the obviousness rejections. However, this case does not support the obviousness rejections here.

The claims at issue in *Boesch* were directed to specific nickel alloys consisting essentially of specific metals in specific amounts. The recited amounts fell within ranges of amounts disclosed in the prior art. The Board upheld the obviousness rejection on the basis that the “discovery of an optimum value of a result effective variable in a known process in ordinarily within the skill of the art.” This rationale does not apply here for at least several reasons.

First, the claims on appeal are method claims, not composition claims. Second, the recited methods are not “a known process.” Third, the recited dosage does not fall within a range taught in the art to be effective for the treatment of thermoregulatory dysfunction associated with menopause. As shown above, the cited references do not suggest the claimed methods or provide any reasonable expectation of success in being able to treat thermoregulatory dysfunction associated with menopause using 7/5 mg/day paroxetine mesylate.

*Boesch* also is distinguishable on other grounds. While *Boesch*’s evidence of unexpected results was found to be not commensurate with the scope of its claims, Appellant’s evidence of unexpected results is fully commensurate with the scope of the claims on appeal, as discussed above.

For at least these reasons, *In re Boesch* does not govern the issues on appeal or support the pending obviousness rejections.

**B. THE DEPENDENT CLAIMS ARE NOT OBVIOUS**

The Advisory Action mailed May 31, 2011 sets forth separate rejections of dependent claims 20 and 21. These claims are not obvious over the cited references for at least the following reasons.

*1. Combining Stearns (2005), Gould, and Barnes (U.S. 4,721,723) Does Not Make Out A Prima Facie Case Of Obviousness of Claim 20*

Claim 20 is directed to embodiments of independent claim 13 where the paroxetine mesylate is in a crystalline form. The combination of Stearns (2005), Gould, and Barnes does not make out a prima facie case of obviousness of these embodiments.

Barnes is directed to a specific form of crystalline paroxetine hydrochloride hemihydrate. Barnes does not disclose any form of paroxetine mesylate or any method of treating thermoregulatory dysfunction associated with menopause.

The inability of Stearns (2005) and Gould to render obvious the subject matter of claim 13 is shown above. Combining Barnes with Stearns (2005) and Gould does not remedy or overcome the inability of these references to teach or suggest the claimed methods, or provide the reasonable expectation of success required to support an obviousness rejection.

Moreover, Barnes does not even suggest the specific feature recited in claim 20, crystalline paroxetine mesylate, because it relates solely to crystalline paroxetine hydrochloride hemihydrate. The Examiner has not put forth any reasoning or evidence as to why Barnes' disclosure of crystalline paroxetine hydrochloride hemihydrate renders obvious a crystalline form of paroxetine mesylate. As set forth in MPEP § 2141, "[t]he key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious." Indeed, the Supreme Court in *KSR* noted that the analysis supporting an obviousness rejection "should be made explicit." *KSR*, 124 S. Ct. at 1741. Here, where the Examiner has provided no such rationale, the Examiner has not met the burden of establishing a prima facie case of obviousness of the subject matter of claim 20.

For at least these reasons, the rejection of claim 20 should be reversed.

2. *Combining Stearns (2005), Gould, and Murthy (U.S. 6,436,956) Does Not Make Out A Prima Facie Case Of Obviousness of Claim 21*

Claim 21 is directed to embodiments of independent claim 13 where the paroxetine mesylate is in an amorphous form. The combination of Stearns (2005), Gould and Murthy does not make out a prima facie case of obviousness of these embodiments.

Murthy is directed to an amorphous form of paroxetine hydrochloride (anhydrous). Murthy does not disclose any form of paroxetine mesylate or any method of treating thermoregulatory dysfunction associated with menopause.

The inability of Stearns (2005) and Gould to render obvious the subject matter of claim 13 is shown above. Combining Murthy with Stearns (2005) and Gould does not remedy or overcome the inability of these references to teach or suggest the claimed methods, or provide the reasonable expectation of success required to support an obviousness rejection.

Moreover, Murthy does not even suggest the specific feature recited in claim 21, paroxetine mesylate in an amorphous form, because it relates solely to amorphous paroxetine hydrochloride (anhydrous). The Examiner has not put forth any reasoning or evidence as to why Murthy's disclosure of amorphous paroxetine hydrochloride (anhydrous) renders obvious an amorphous form of paroxetine mesylate. Thus, the Examiner has not met the burden of establishing a prima facie case of obviousness of the subject matter of claim 21. See *KSR*, 124 S. Ct. at 1741; MPEP § 2141.

For at least these reasons, the rejection of claim 21 should be reversed.

**C. CONCLUSION**

For at least the forgoing reasons, all pending obviousness rejections should be reversed.

Respectfully submitted,

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**VIII. CLAIMS APPENDIX**

13. A method for treating a patient suffering from a thermoregulatory dysfunction associated with menopause comprising administering paroxetine mesylate to said patient in an amount, based on the paroxetine moiety, of 7.5 mg/day.

15. The method of claim 13, wherein said thermoregulatory dysfunction is a condition selected from the group consisting of hot flashes, hot flushes, night sweats and combinations thereof.

20. The method of claim 13, wherein the paroxetine mesylate is in a crystalline form.

21. The method of claim 13, wherein the paroxetine mesylate is in an amorphous form.

22. A method for treating a patient suffering from a thermoregulatory dysfunction associated with menopause comprising administering paroxetine to said patient, wherein said paroxetine is in the form of a pharmaceutically acceptable mesylate salt, in amorphous or crystalline form, and mixtures thereof, wherein said paroxetine mesylate is administered in an amount, based on the paroxetine moiety, of 7.5 mg/day.

**IX. EVIDENCE APPENDIX**

1. Stearns et al., *Annals of Oncology* 11: 17-22 (2000), submitted by Appellant in the Information Disclosure Statement filed December 1, 2008 and cited in the Office Action mailed August 17, 2010.
2. Stearns et al., *Journal of Clinical Oncology* 23: 6919-30 (October 1, 2005), submitted by Appellant in the Information Disclosure Statement filed December 1, 2008 and cited in the Office Action mailed August 17, 2010.
3. Jenkins, U.S. Patent 6,369,051, submitted by Appellant in the Information Disclosure Statement filed December 1, 2008 and cited in the Office Action mailed August 17, 2010.
4. Gould et al., *International Journal of Pharmaceutics* 33: 201-17 (1986), cited in the Office Action mailed December 8, 2010.
5. Murthy et al., U.S. Patent 6,436,956, submitted by Appellant in the Information Disclosure Statement filed December 1, 2008 and cited in the Office Action mailed December 8, 2010.
6. Barnes et al., U.S. Patent 4,721,723, submitted by Appellant in the Information Disclosure Statement filed December 1, 2008 and cited in the Office Action mailed December 8, 2010.
7. Rule 132 Declaration of Dr. Lippman submitted by Appellant with the Response filed September 22, 2010, and acknowledged in the Office Action mailed December 8, 2010.
8. Loprinzi, et al., *Mayo Clinic Proc.* 79: 1247-51 (2004), submitted by Appellant in the Information Disclosure Statement submitted December 1, 2008 and acknowledged in the Office Action mailed August 17, 2010 on initialed form SB/08.

1 RECORD OF ORAL HEARING

2  
3 UNITED STATES PATENT AND TRADEMARK OFFICE

4  
5  
6 BEFORE THE PATENT TRIAL AND APPEAL BOARD

7  
8  
9 *Ex parte* PATRICIA ALLISON TEWES RICHARDS

10  
11  
12 Appeal 2012-004394  
13 Application 12/292,960  
14 Technology Center 1600

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16  
17 Oral Hearing Held: October 15, 2013  
18  
19

20  
21 Before DONALD E. ADAMS, ERIC B. GRIMES, and  
22 ERICA A. FRANKLIN, *Administrative Patent Judges*.

23  
24 APPEARANCES:

25  
26 ON BEHALF OF THE APPELLANT:

27  
28 COURTENAY C. BRINCKERHOFF, ESQUIRE  
29 Foley & Lardner, L.L.P.  
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32 Washington, D.C. 20007  
33

34 The above-entitled matter came on for hearing on Tuesday, October 15, 2013, at 9  
35 a.m., at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria,  
36 Virginia, before Julie Souza, Notary Public.  
37  
38

Appeal 2012-004394  
Application 12/292,960

P R O C E E D I N G S

- - - - -

THE USHER: Good morning. Calendar No. 29, appeal number 2012-4394,  
Ms. Brinckerhoff.

JUDGE ADAMS: Thank you.

THE USHER: You're welcome.

JUDGE ADAMS: Good morning, Ms. Brinckerhoff.

MS. BRINCKERHOFF: Good morning.

JUDGE ADAMS: We're familiar with your record. You have 20 minutes  
and you can begin when you're ready. If you want to introduce your colleagues,  
that'd be great.

MS. BRINCKERHOFF: Thank you. I'm Courtenay Brinckerhoff from  
Foley & Lardner. With me today is Jay Coleman (phonetic) from the applicant  
Noven and Dan Shelton, he's also from Foley & Lardner.

The claims on appeal relate to methods of treating menopause associated hot  
flashes by administering 7.5 milligrams per day of Paroxetine Mesylate. This  
therapy recently was approved by the FDA for Noven products, Brisdelle.  
Brisdelle is the first non-hormonal therapy approved by the FDA for the treatment  
of hot flashes.

The examiner rejected the independent claims for alleged obviousness over  
the Stearns 2000 paper in combination with Jenkins and Gould, or over the Stearns  
2005 paper in combination with Gould.

The premise of Dr. Stearns's paper disclosed the use of Paroxetine  
Hydrochloride to treat hot flashes and that it would have been obvious to replace  
the Hydrochloride with the Mesylate and optimize the dose of Paroxetine to reduce  
side effects in light of the recited method.

Appeal 2012-004394  
Application 12/292,960

1           However, there was never a reasonable expectation of success that a dose  
2     lower than the 10 milligram lower dose tested by Paroxetine, I'm sorry, tested by  
3     Stearns, would be effective and that no expectation that that dose can be slashed by  
4     a further 25 percent and still be effective against hot flashes. And, in this context,  
5     it's important to understand that efficacy and (indiscernible) hot flashes only can be  
6     tested empirically. There's no inner local (phonetic) marker or physiological  
7     marker for efficacy. Efficacy only can be shown by a clinical trial in the individual  
8     patient (indiscernible).

9           As you can see in the Stearns paper, there's no discussion of  
10    pharmacokinetic of the target (indiscernible) for the drug and no correlation of  
11    pharmacokinetic to, other than therapeutic effect.

12          In this way, the situation is similar to that (indiscernible) Federal Circuit in  
13    the 2012 decision in In Re Cyclobenzaprine Hydrochloride Extended Release  
14    Capsule Patent Litigation. In that case, the Federal Circuit found that the extended  
15    release compositions were not obvious over the independent compositions. There  
16    was no correlation between pharmacokinetics drug Farbilo (phonetic) and  
17    pharmacodynamics efficacy, so even though it might have been obvious approach  
18    to try to model the extended release formulation on the immediate release  
19    pharmacokinetics, there was no expectation that would succeed.

20          JUDGE ADAMS: So when we have Jenkins that would suggest a dosage  
21    from .1 mgs per day to about 500 mgs per day, why wouldn't that suggest that it's  
22    just routine optimization?

23          MS. BRINCKERHOFF: Well we really don't think that Jenkins supports the  
24    rejection and it doesn't provide any teaching that could provide an expectation of  
25    success in this regard. Jenkins is directed to combination therapies for a laundry  
26    list of conditions that use a substituted indole compound with an SSRI --

Appeal 2012-004394  
Application 12/292,960

1 JUDGE ADAMS: If I can just stop you there, yours doesn't exclude a  
2 combination therapy. Is that right?

3 MS. BRINCKERHOFF: That's correct though --

4 JUDGE ADAMS: Okay.

5 MS. BRINCKERHOFF: -- the same as (indiscernible) are comprising  
6 (phonetic).

7 JUDGE ADAMS: Okay. Go ahead.

8 MS. BRINCKERHOFF: So the sentence of Jenkins cited by the examiner  
9 says, "Effective administration of these compounds may be given at an effective  
10 dose from about .1 mgs per day to about 500 mgs per day." As explained in our  
11 briefs and evident from reading Jenkins, it's not clear whether this sentence refers  
12 to a substituted indole compound or to the SSRI drug.

13 JUDGE ADAMS: So when it says these compounds, what is it speaking to?

14 MS. BRINCKERHOFF: The way I read it, it follows more naturally from  
15 the discussion of the indole compound.

16 JUDGE ADAMS: Why would you say that? I mean the foregoing  
17 paragraph discusses these compounds in the context of SSRIs and indole  
18 compounds.

19 MS. BRINCKERHOFF: Well when it clearly talks about SSRI at column --  
20 at column 16, it says that the SSRI should be administered in regimen and at doses,  
21 dosages known in the art.

22 JUDGE ADAMS: No, it says they may be administered in regimens that  
23 people naturally dose themselves.

24 MS. BRINCKERHOFF: Well and then when it talks about Paroxetine in  
25 particular it specifically talks about 20 to 50 milligrams. That's again at column  
26 16.

Appeal 2012-004394  
Application 12/292,960

1 JUDGE ADAMS: Again, it may be administered at the dosages that are  
2 known in the art.

3 (Pause).

4 MS. BRINCKERHOFF: Sorry, he's going to find the -- the -- the sentence  
5 that has it in my notes correctly.

6 Jenkins, as I mentioned, has a laundry list of compounds so from column  
7 one or column three, there's a laundry list of conditions that can be treated from  
8 depression, anxiety, obesity, chronic fatigue syndrome, attention deficit disorder,  
9 and included in that list is hot flashes.

10 JUDGE ADAMS: Correct.

11 MS. BRINCKERHOFF: So the skilled person reading this, the patent as a  
12 whole, would not understand Jenkins to be teaching that any of its compounds, any  
13 of its, even if you take it to mean the SSRIs, that any of the SSRIs would be  
14 effective against any of these conditions at any dose within that range. There's just  
15 no, there's no expectation of success (indiscernible).

16 JUDGE ADAMS: Now -- now that you have column 16, if you could take a  
17 look at line 53 and -- and read that sentence for me, 53 to 56 of column, excuse me,  
18 of column 15.

19 MS. BRINCKERHOFF: "It's preferred that the administration?"

20 JUDGE ADAMS: Yes, that sentence --

21 MS. BRINCKERHOFF: "It's preferred that the administration of one or  
22 more of the SSRIs and subsequent indole compounds (indiscernible) begin at a  
23 lower dose and be increased until the desired effects are achieved."

24 JUDGE ADAMS: So Jenkins speaks to treating, among other things, hot  
25 flashes. Jenkins speaks to administering hot flashes with an SSRI which Jenkins  
26 says could be your particular drug in -- in combination with an indole compound,

Appeal 2012-004394  
Application 12/292,960

1 and it says that we prefer you start at the lowest dose possible and then increase  
2 that dosage until you see an effect that's therapeutically efficacious. Then he tells  
3 us in the very next sentence, do you want to read that into the -- the record for us.

4 MS. BRINCKERHOFF: "Effective administration of the compounds may  
5 be an effective dose of from about .1 to about 500."

6 JUDGE ADAMS: Okay. So what's your argument?

7 MS. BRINCKERHOFF: So the argument is that these are derived  
8 (phonetic) general teachings and they don't give any reasonable expectation of  
9 success, that a dosage of as low as 7.5 milligrams per day would be effective.  
10 Even if you take Jenkins's guidance that you should start at a low dose and  
11 increase, that would blend right into the Stearns papers which taught that the low  
12 dose was ten milligrams, that some patients might see a benefit or might respond at  
13 ten milligrams per day and that you should start at ten and go higher to twenty, or  
14 even higher than twenty for some patients.

15 JUDGE ADAMS: No, I think that particular Stearns reference states that  
16 this is a pilot trial and we weren't here to speak to what the optimum dosage was.  
17 Is that correct?

18 MS. BRINCKERHOFF: So there's two Stearns papers. The -- the first, the  
19 -- the 2000 paper (indiscernible) --

20 JUDGE ADAMS: Let's not confuse the two. The Stearns paper that is  
21 relied upon in combination with Jenkins. It says that it's just a trial and we use ten  
22 milligrams per day and twenty milligrams per day, but we didn't -- we didn't get  
23 into what the best dosage would be. We just have those two dosages.

24 MS. BRINCKERHOFF: But in that context they say it's possible that ten  
25 might be sufficient and it's possible that women who do not respond to twenty

Appeal 2012-004394  
Application 12/292,960

1 might benefit from a further increased dose. There's no suggestion that you should  
2 go lower than ten.

3 JUDGE ADAMS: So at page 21 of the Stearns document.

4 MS. BRINCKERHOFF: Right. So the pilot trial cannot answer questions  
5 related to the optimum dose.

6 JUDGE ADAMS: Okay.

7 MS. BRINCKERHOFF: And then the third sentence --

8 JUDGE ADAMS: In -- in Stearns, in this paper it spoke to this idea of side  
9 effects. Is that right?

10 MS. BRINCKERHOFF: Yes.

11 JUDGE ADAMS: And it spoke to the -- the ten milligram per day might be  
12 better at alleviating these adverse side effects than the twenty milligram per day. Is  
13 that right?

14 MS. BRINCKERHOFF: Right. We don't -- we don't argue that reducing  
15 the dose would likely reduce side effects. The question is that there's no  
16 expectation that he would reduce the side effects while failing (phonetic) any  
17 efficacy.

18 JUDGE ADAMS: So you, your suggestion then is that since there's not a  
19 reference of record that says, for example, five milligrams per day was effective in  
20 treating hot flashes, there's no expectation that reading from the minimum dosage  
21 that Stearns used which was ten milligrams per day down to maybe 7.5 milligrams  
22 per day would be efficacious, notwithstanding Jenkins disclosure.

23 MS. BRINCKERHOFF: We don't think there was any reasonable  
24 expectation of success in -- in that regard, with regard to the 7.5 milligrams per  
25 day, and I think even if you start with Jenkins and Jenkins is discussing the use of  
26 the conventional doses of these SSRIs which, for Paroxetine, Jenkins teaches that

Appeal 2012-004394  
Application 12/292,960

1 20 50, and Stearns also started with that 20 and, in Stearns's mind, starts tests at the  
2 low dose which was ten, and found that the low dose might be effective, might be  
3 effective, and that people --

4 JUDGE ADAMS: Well --

5 MS. BRINCKERHOFF: -- who didn't respond after 20 --

6 JUDGE ADAMS: -- were these drugs at the art recognized dosage ten and  
7 twenty, are those for treating hot flashes or are those for treating something else?

8 MS. BRINCKERHOFF: Our -- our current product is the first product that  
9 was for treating hot flashes.

10 JUDGE ADAMS: And Stearns at the time --

11 MS. BRINCKERHOFF: So that the 20 milligram --

12 JUDGE ADAMS: -- at the time of Stearns publication that the ten and  
13 twenty milligram per day was useful for treating --

14 MS. BRINCKERHOFF: The 20 milligrams and higher was used for treating  
15 the depression.

16 JUDGE ADAMS: Okay.

17 MS. BRINCKERHOFF: Depression and anxiety. So this was a new  
18 exploration of trying to find a non-hormonal treatment for hot flashes.

19 JUDGE ADAMS: Uh-huh.

20 MS. BRINCKERHOFF: Because of the problems with hormonal treatments  
21 and the risk of breast cancer. As reflected, I think, in the 2005 Stearns paper,  
22 people were testing a lot of different SSRIs and there's been a lot of experimental,  
23 experiment and failure, in this regard which is why this product is a significant  
24 advantage.

25 JUDGE ADAMS: Well the Stearns 2005 paper basically says the same  
26 thing. When compared against placebo, folks who were treated with ten mgs per

Appeal 2012-004394  
Application 12/292,960

1 day versus twenty mgs per day preferred the ten mgs per day because of the  
2 reduction in adverse side effects along with the corresponding treatment of hot  
3 flashes for these menopausal women. Is that right?

4 MS. BRINCKERHOFF: That's right, and that's why they recommend  
5 starting with a low dose of ten and testing higher in people that respond --

6 JUDGE ADAMS: Okay.

7 MS. BRINCKERHOFF: -- and I think when you look at Stearns 2005, they  
8 also emphasize that they haven't (indiscernible) escalating doses of Paroxetine and  
9 aren't sure about recommending even higher doses. But there's no suggestion that  
10 you should start lower than the ten.

11 JUDGE ADAMS: No suggestion in your mind to optimize, to get the best  
12 dosage. Is that right?

13 MS. BRINCKERHOFF: Excuse me?

14 JUDGE ADAMS: No suggestion according to your arguments to get the --  
15 the optimal dosage?

16 MS. BRINCKERHOFF: Well there's no reasonable expectation that the  
17 dose as low as 7.5 would be effective, so the doses that, the lower dose of Stearns  
18 was 33 percent higher than our dose, and there's just no expectation that you could  
19 slash it by as much as we did and still be effective.

20 UNIDENTIFIED SPEAKER: The only way to optimize or actually prove  
21 efficacy is to run a trial. As much as optimization, which I don't think is the issue  
22 here, can be done, you have to run, practically speaking, every dosage in that range  
23 --

24 JUDGE ADAMS: Well if Jenkins would suggest a broad range and you  
25 have something close as suggested by Stearns, why would you say it's not  
26 optimization?

Appeal 2012-004394  
Application 12/292,960

1 UNIDENTIFIED SPEAKER: Because it's a shot in the dark.

2 MS. BRINCKERHOFF: And I don't think -- I don't think -- I don't think  
3 Stearns is close when you look at the percentages as recited. It's cutting, it's either,  
4 it's 25 percent lower than what Stearns cited.

5 JUDGE ADAMS: But -- but Jenkins would suggest that you use the lowest  
6 minimum dose, preferably use the lowest minimum dose that works.

7 MS. BRINCKERHOFF: I mean that's almost -- that's -- that's -- almost a --

8 JUDGE ADAMS: And whether it's a trial or not, that's what the suggestion  
9 would be.

10 MS. BRINCKERHOFF: I mean that's almost a universal truth, right? When  
11 you're medicating someone, you want to use the lowest dose that works. That's --  
12 that's -- that's not really adding to the body of knowledge in this context.

13 We really think that Jenkins just is, you know, it teaches a really broad  
14 range. It doesn't provide any specific guidance. It teaches a laundry list of  
15 conditions to be treated. It teaches a variety of SSRIs and out of its SSRI list,  
16 when it does talk about Paroxetine, it talks about 20 to 50.

17 JUDGE ADAMS: Well again, it's says that you may be able to use these at  
18 the art recognized dosage. Correct?

19 MS. BRINCKERHOFF: But that's the only guidance it's giving someone  
20 skilled in the art specifically when they get down to it.

21 JUDGE ADAMS: What that --

22 MS. BRINCKERHOFF: There's --

23 JUDGE ADAMS: -- what that SSRIs are known to be useful, they're known  
24 -- known to those of ordinary skill in the art and they're known at particular  
25 dosages? And you -- and --

26 MS. BRINCKERHOFF: But it says the SSRI compounds may be used --

Appeal 2012-004394  
Application 12/292,960

1 JUDGE ADAMS: -- and -- and if I -- if I -- if I can finish, and that those  
2 particular dosages are known to those of ordinary skill in the art and that you can  
3 use those particular dosages, notwithstanding what we say in the column directly to  
4 the left of that which says, "Preferably we start at the minimum dose which ranges,  
5 which our effective administration of these compounds may be at an effective dose  
6 of .1 to about 500 mgs per day for the treatment of, among other things, hot  
7 flashes."

8 MS. BRINCKERHOFF: It -- it -- it really does not give any expectation of  
9 success --

10 JUDGE ADAMS: Okay.

11 MS. BRINCKERHOFF: -- that --

12 JUDGE ADAMS: We've -- we've been around this for 15 minutes or so. Is  
13 there any other argument that you wanted to make before your time expires?

14 MS. BRINCKERHOFF: Again, I think it's important to realize that the --  
15 that it's unpredictable, the treatment of hot flashes. Perhaps in contra-distinction to  
16 the other conditions mentioned in Jenkins, there is no relationship or known  
17 relationship between the pharmacokinetic level and efficacy, and there was no  
18 expectation that the dose as low as 7.5 milligrams would be effective.

19 Just, legally, again patentability and circumstances like this is supported by  
20 the In Re Cyclobenzaprine case that I mentioned previously that was decided last  
21 April and our reply brief was in, and also the Eli Lilly case that is in our -- in our  
22 briefs where, even if it might have been obvious to try a certain approach, unless  
23 there was a reasonable expectation of success, it's not obvious.

24 JUDGE ADAMS: Okay. Any questions? Questions? All right, thank you  
25 for your time.

26 MS. BRINCKERHOFF: Thank you.

Appeal 2012-004394

Application 12/292,960

1 (Whereupon, these proceedings were concluded.)

# EXHIBIT 41

US 20040067254A1

(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0067254 A1**  
(43) **Pub. Date: Apr. 8, 2004**  
**Lemmens et al.**(54) **PAROXETINE COMPOSITIONS AND  
PROCESSES FOR MAKING THE SAME****Related U.S. Application Data**(76) Inventors: **Jacobus M. Lemmens**, Mook (NL);  
**Theodorus H. A. Peters**, Arnhem (NL);  
**Frantisek Picha**, Brno (CZ); **Johannes  
J. Platteeuw**, 's-Hertogenbosch (NL);  
**Frans van Dalen**, Nijmegen (NL)(62) Division of application No. 09/939,561, filed on Aug.  
28, 2001, now Pat. No. 6,645,523.(60) Provisional application No. 60/228,110, filed on Aug.  
28, 2000. Provisional application No. 60/234,936,  
filed on Sep. 26, 2000.**Publication Classification**Correspondence Address:  
**MARK R. BUSCHER**  
**P.O. BOX 161**  
**CATHARPIN, VA 20143 (US)**(51) **Int. Cl.<sup>7</sup>** ..... **A61K 31/137**; A61K 9/20(52) **U.S. Cl.** ..... **424/465**; 514/649(57) **ABSTRACT**

Paroxetine salt compositions having improved stability are formed by controlling the pH to 6.5 or less. The compositions can be made with the aide of water without significant coloration problems. The paroxetine salts include paroxetine hydrochloride salts but preferably use paroxetine sulfonate salts such as paroxetine methane sulfonate.

(21) Appl. No.: **10/678,082**(22) Filed: **Oct. 6, 2003**

US 2004/0067254 A1

Apr. 8, 2004

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# PAROXETINE COMPOSITIONS AND PROCESSES FOR MAKING THE SAME

## CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) from prior U.S. provisional application serial No. 60/228,110 filed Aug. 28, 2000 and from prior U.S. provisional application serial No. 60/234,936 filed Sep. 26, 2000; the entire contents of each of the aforementioned provisional applications being incorporated herein by reference.

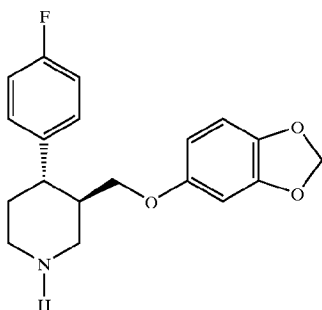
## BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] The present invention relates to a paroxetine compositions, especially pharmaceutical formulations and dosage forms, and to processes of manufacturing the same.

[0004] 2. Description of the Related Arts

[0005] U.S. Pat. No. 4,007,196 describes certain compounds that possess anti-depressant activity. One specific compound mentioned in this patent is known as paroxetine and is represented by the following formula:

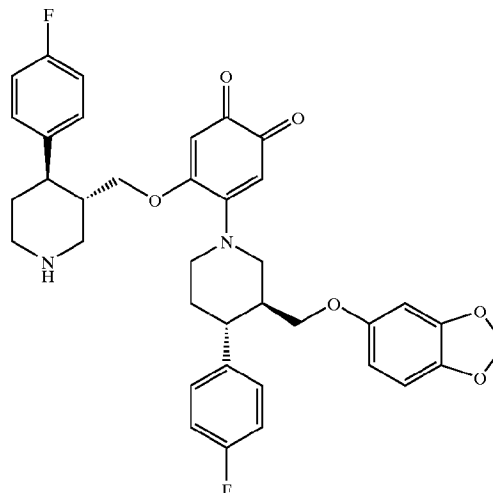


[0006] Paroxetine has been approved for treating, inter alia, depression in humans and is being marketed around the world under such brand names as Paxil® (SmithKline Beecham) and Seroxat. Dosage forms thus far include immediate release tablets, extended release tablets, capsules and suspensions. The active substance in all commercial forms thus far has been paroxetine hydrochloride and specifically with regard to tablets and other solid forms the active has been paroxetine hydrochloride hemihydrate as disclosed in U.S. Pat. No. 4,721,723 and EP 223403.

[0007] WO 95/16448 reports that all commercial paroxetine hydrochloride hemihydrate tablets were, at least up until that time, made using a wet granulation process. Further, the commercial tablets exhibited a color change; i.e., these tablets often developed a pink hue that is highly undesirable. This was apparently masked in the commercial product by a colored outer coat layer. The point of the PCT publication is that the pink hue formation can be avoided by carrying out tableting in the absence of water, i.e. by conventional dry granulation and direct compression. The PCT publication does not mention what the coloring compound(s) are or their route of formation. But, subsequent

documents reveal that the coloration problem involves the formation of a coloring impurity identified below as the compound of formula A.

A



[0008] Since the publication of WO95/16448, it appears that the brand name paroxetine hydrochloride hemihydrate product in Europe, at least, was changed to a dosage form made by a dry granulation technique in accordance with the teachings in the PCT publication.

[0009] It would be advantageous to find a paroxetine composition that does not suffer from coloration or that is less prone to coloration regardless of how the composition is made. Further, it would be desirable to make a paroxetine composition with the aid of water, such as by wet granulation, that nonetheless was not prone to the above-mentioned coloration problems.

[0010] In particular, the application of an aqueous granulation process for industrial scale production is desirable in that such a process provides uniform distribution of the active substance within the bulk granulate composition so that the dose uniformity of tablets or capsules is more easily assured. This is especially true in the case of unit dosage forms containing a low dose of a potent active agent. Here, paroxetine is normally used in 20 to 40 mg per tablet and thus its uniformity in large scale production could be of concern. Water is a very suitable solvent for the granulation process because it is non-toxic and non-flammable. Thus, it would be desirable to find a way to use an aqueous granulation process for the industrial scale production of paroxetine final forms that would also avoid or limit the occurrence of the color forming impurities.

[0011] U.S. Pat. No. 5,874,447 describes paroxetine sulfonate salts, including paroxetine methane sulfonate also known as paroxetine mesylate. These sulfonate salts have advantageous properties in comparison to the known salts, including the hydrochloride salts. For example, the sulfonate salts have high water solubility and good thermal stability, making them useful in forming a commercial paroxetine dosage form. The U.S. Pat. No. 5,874,447 patent discloses

US 2004/0067254 A1

Apr. 8, 2004

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that tablets can be made by any known method including a dry technique (direct compression, dry granulation) or a wet technique (wet granulation). However, no discussion appears in the 5,874,447 patent regarding the paroxetine hydrochloride coloring problem.

#### SUMMARY OF THE INVENTION

[0012] Now, it has surprisingly been discovered that solid paroxetine compositions including granulates and dosage forms made therefrom, can be made more stable against coloration, even if made with the aid of water such as by an aqueous granulation process, by controlling the pH of the composition to 6.5 or less. Further, it appears that paroxetine sulfonate salts are less prone to coloration problems than paroxetine hydrochloride salts, even if made with the assistance of water. Studies by the present inventors reveal that the impurity A is a dimer formed from the paroxetine free base in an aqueous alkaline environment. Oxygen is also apparently needed to allow the dimer reaction to proceed. Given the discovery that coloring impurity A is formed in the presence of water, it is understandable in hindsight how carrying out a dry process as suggested in WO95/16448 would help to minimize and/or avoid coloration; i.e. the required aqueous medium for forming the dimeric impurity is missing thereby inhibiting its formation. Having elucidated the source of the coloring problem, the present invention provides a novel solution thereto by keeping the pH of the composition to 6.5 or less. Alternatively, the present invention unexpectedly solves the coloring problem by switching the paroxetine salt from hydrochloride to sulfonate and thereby allowing the use of water in the preparation of paroxetine granules without incurring any substantial coloration.

[0013] Thus, in a first aspect of the invention, there is provided a solid paroxetine composition comprising a paroxetine salt and an excipient wherein said composition has a pH of 6.5 or less, as is hereinafter defined. The paroxetine salt is preferably a paroxetine sulfonate salt such as paroxetine methane sulfonate or a paroxetine hydrochloride salt. The excipients generally include a binder or diluent such as calcium phosphate or microcrystalline cellulose as well as a disintegrant and lubricant. The composition can be an intermediate form or a final dosage form such as a tablet or capsule. In one embodiment, a tablet is made that does not need a taste masking coating to avoid the usual bitter taste associated with paroxetine compositions.

[0014] A second aspect of the present invention relates to paroxetine solid dosage forms comprising a paroxetine sulfonate salt as a pharmaceutically active agent and having been made with the aid of water. The solid dosage form can be a tablet, pellet or capsule form, etc., and contains a pharmaceutically effective amount of paroxetine sulfonate, e.g. for treating depression, obsessive-compulsive disorder, or panic attack, etc. Preferably the excipients are selected so that the composition has a pH of 6.5 or less. Further, the composition is normally dried to a sufficient extent that the total content of added water remaining is 2.0 wt % or less, preferably 1.3 wt % or less, and more preferably 1.0 wt % or less. Generally, the composition does not contain any decolorization agent as an excipient. Even though an aqueous process is used, the dosage form of the present invention exhibits no, or substantially no, formation of a pink or other colored hue.

[0015] A third aspect of the invention provides for a granulate formed by mixing water, paroxetine sulfonate salt, and at least one excipient and drying the resulting mixture. Typically the water and paroxetine sulfonate salt are provided together as an aqueous solution and added to the powdered or dry excipient(s), although this is not required. In some embodiments, the excipient(s) may be pre-blended and granulated such as by a dry granulation technique before being contacted with a concentrated aqueous paroxetine sulfonate salt solution. The mixture is dried to form a granulate to which additional excipients may be added, if desired. The granulate can be formed into other conventional dosage forms such as tablets, capsules, sachets, pellets, etc. The composition is preferably selected as described above for the dosage forms, namely with a pH of 6.5 or less and with an added water content of 2.0 wt % or less.

[0016] A fourth aspect of the invention provides a process for making pharmaceutical compositions which comprises mixing paroxetine sulfonate and at least one excipient with the aid of water. In one convenient embodiment, an aqueous solution containing at least 10 wt % of a paroxetine sulfonate salt is added to at least one solid excipient and dried to form a granulate. Preferably, the aqueous solution is a highly concentrated aqueous solution of paroxetine sulfonate salt having a concentration of not less than 30 wt %. This process can be used advantageously to form the granulates described above which can be subsequently processed into the above-described dosage forms. Alternatively, water can be added to a powder bed of paroxetine sulfonate and one or more excipients and the mixture dried to form granules.

[0017] A preferred paroxetine sulfonate salt for use in all aspects of the present invention is paroxetine methane-sulfonate, also called paroxetine mesylate. Paroxetine mesylate is compatible with many common pharmaceutical excipients useful in aqueous granulation procedures, which makes the process reliable on an industrial scale.

#### DETAILED DESCRIPTION OF THE INVENTION

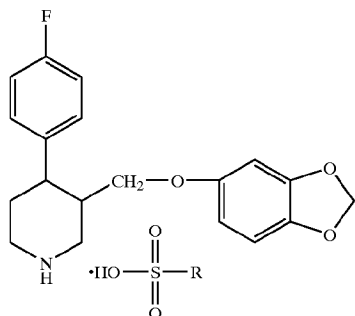
[0018] The present invention relates to solid paroxetine compositions that resist the formation of a color hue and to processes for making the same with the aid of water. As used herein, the expression "made with the aid of water" means that water is added during some aspect of the formation process of the composition but is substantially or completely removed in the final composition. The water can be added to excipients, to the paroxetine salt especially paroxetine sulfonate salts, or to both. The solid compositions of the invention include solid dosage forms such as tablets, capsules, sachets, etc., and intermediate forms such as granules or pellets.

[0019] Paroxetine salts used in the present invention are pharmaceutically acceptable salts, i.e., acid addition salts. Preferred salts include paroxetine hydrochloride salts and paroxetine sulfonate salts. The paroxetine hydrochloride salt can be of any form including the paroxetine hydrochloride hemihydrate form and paroxetine hydrochloride anhydrate forms. The paroxetine sulfonate salts used in the present invention can be any salt of paroxetine where the anion contains a sulfonate group; i.e. the moiety  $-S(O_2)OH$ . Preferred sulfonate salts include those having the following structural formula:

US 2004/0067254 A1

Apr. 8, 2004

3



[0020] wherein R represents a C<sub>1</sub>-C<sub>10</sub> substituted or unsubstituted alkyl group or a substituted or unsubstituted aromatic group wherein the substituents are selected from the group consisting of C<sub>1</sub>-C<sub>10</sub> alkyl, halogen, nitro, hydroxy, alkoxy, and combinations thereof. Preferred paroxetine sulfonate salts include those having a solubility in water of at least 100 mg/l ml of water. Particularly preferred sulfonate salts include methanesulfonate, ethanesulfonate, benzenesulfonate and p-toluenesulfonate salt forms.

[0021] An "excipient" as used herein means any pharmaceutically acceptable inactive component of the composition. As is well known in the art, excipients include diluents, binders, lubricants, disintegrants, colorants, preservatives, pH-adjusters etc. The excipients are selected based on the desired physical aspects of the final form: e.g., obtaining a tablet with desired hardness and friability, being rapidly dispersible and easily swallowed, etc. The desired release rate of the active substance from the composition after its ingestion also plays a role in the choice of excipients.

[0022] Suitable excipients for use in this invention include:

[0023] a diluent such as calcium hydrogen phosphate, lactose, mannitol etc.

[0024] a binder such as microcrystalline cellulose or a modified cellulose, povidone etc.

[0025] a disintegrant such as sodium starch glycolate, croscopolvidone

[0026] a lubricant such as magnesium stearate, sodium stearyl fumarate

[0027] a colorant, taste masking agent etc.

[0028] It is particularly advantageous that the composition of the invention is not specifically required to use anhydrous excipients or hydrophobic excipients, although such excipients may be used. Similarly, the present invention does not have to strictly control the water content in the excipients prior to their use or incorporation. In a preferred embodiment, no decolorization agent is required to be present in the composition of the invention, although such may be present if desired. "Decolorization agent" as used herein means an agent which is being added to a composition with the aim to protect the active substance against reactions that form colored products, such as an antioxidant (e.g. ascorbic acid etc.), free radical scavenger (e.g. tocopherol etc.) etc.

[0029] It has now been discovered that the undesired impurity A is preferentially formed in an aqueous alkaline environment from the paroxetine free base. Accordingly, it can be advantageous to employ multiple strategies to reduce or prevent coloration. These strategies include limiting the amount of added water remaining in the composition, controlling the pH of the composition to be sufficiently acidic, limiting the presence of oxygen during formation and/or storage, and reducing the level of paroxetine free base impurity in the active. Indeed, using one or more of these strategies can control the coloring problem encountered with other paroxetine salt forms including paroxetine hydrochloride salt forms, whether made from a dry or wet process. For example controlling the pH to 6.5 or less, controlling (reducing) the level of free base impurity, and/or quickly removing 98% or more of the water used in granulating should allow for the formation of a color stable paroxetine hydrochloride pharmaceutical composition. Additionally, for reasons that are not entirely clear, paroxetine sulfonate salts can provide superior color stability in comparison to paroxetine hydrochloride salts.

[0030] The compositions of the present invention, including granulates and final dosage forms, preferably have a pH of 6.5 or less, more preferably a pH of 6.0 or less, including about 5.5 or less. Typically, the pH of the dosage form or a granulate is within the range of 4.5 to 6.5, more typically from 5.0 to 6.0. The pH is determined by forming a slurry of the solid composition with water and measuring the pH of the slurry, as is understood by workers skilled in the art regarding the pH of a solid composition. The concentration of the composition in the slurry is 20 wt %. The pH is measured by any standard technique. The pH can be adjusted by the proper selection of excipients.

[0031] In this respect, a proper grade of calcium phosphate (anhydrous or hydrated) having a pH around 5.5 is preferred to be used as a suitable filler. Commercially available/ pharmaceutically acceptable calcium phosphates are generally alkaline; i.e. pH greater than 7 when measured as described above in a 20% slurry. For instance, DI-TAB, a commercially available dibasic calcium phosphate dihydrate, is reported as having a pH of about 7.4. Nonetheless some forms and grades of calcium phosphate are acidic or neutral pH. This lower pH can be due to the species of calcium phosphate as well as the treatment during processing of the material, such as in removing impurities/washing. For example, dibasic calcium phosphate anhydrous is generally considered to have a pH of about 7.3 whereas A-Tab™ (Rhodia), also a dibasic calcium phosphate anhydrous, has a pH of about 5.1. Further examples of commercially available non-alkaline calcium phosphates include DiCAFOS P (Budenheim) having a pH of about 7 and Fujicalin SG (Fuji) having a pH from 6.1-7.2. By using a non-alkaline calcium phosphate as an excipient, a pharmaceutical composition meeting the desired pH can be attained. Alternatively, a blend of calcium phosphates, even one using acidic and alkaline calcium phosphates, can be used to achieve the desired acidic pH of the composition. The pH can also be assisted by selection of any other excipients in the composition. For instance, another example of a useful acidic excipient is the disintegrant Explotab(TM) of Penwest, which is a cross-linked, low substituted sodium starch glycolate.

ACTBRIS0013646

US 2004/0067254 A1

Apr. 8, 2004

4

[0032] Especially advantageous compositions of the invention comprise paroxetine sulfonate salt in the absence of a hydrosoluble or hydrophilic diluent such as lactose or microcrystalline cellulose. Unlike the suggestions in CH 690 024, wherein such a hydrosoluble/hydrophilic diluent is taught for use with paroxetine mesylate, it has been discovered that surprisingly the use of only a calcium phosphate diluent, such as calcium hydrogen phosphate anhydride, exhibits an additional advantageous feature for industrial application; namely that it efficiently masks or prevents the bitter taste of paroxetine. Thus, after the paroxetine salt, especially paroxetine mesylate, and diluent composition is mixed with a disintegrant and a lubricant and compressed into tablets, the tablets may be administered to a human patient without need of a taste-masking coating or a similar tool for taste masking. To the contrary, the presence of a hydrosoluble or hydrophilic diluent rather pronounces the bitter taste of paroxetine so that such tablet is unpleasant to be swallowed unless film-coated. Pharmaceutical compositions comprising paroxetine methane sulfonate and calcium hydrogen phosphate, optionally containing conventional lubricants and/or disintegrants, form a particular aspect of our invention. Of course, these particular compositions can be made by a dry process (dry mixing followed by direct compression) as well as by any of the wet processes known or described herein, and still provide the unexpected taste masking result.

[0033] In general, the compositions of the present invention preferably have a remaining added water content of 2.0 wt % or less, preferably 1.3 wt % or less, more preferably 1.2 wt % or less, still more preferably 1.0 wt % or less, and most preferably 0.8 wt % or less. The "remaining added water" content refers to the remaining water that was added in the aid of mixing and does not include water that was present in the excipients such as bound water in microcrystalline cellulose. If the composition was made by a dry process, then the remaining added water content is 0.0%. Generally, each formulation has a threshold amount of remaining added water content below which the dimeric impurity A is formed either very little or not at all. Above this threshold amount, the impurity A is formed abundantly. The occurrence of the impurity is thus not usually a linear function of water content. By controlling the added water content in the final granulate, a color stable product can be attained, even if made by a conventional wet granulation process. The same is true for the final product solid dosage form.

[0034] Granules made according to the present invention can be used directly but usually are processed into any of a variety of dosage forms as mentioned above. Typically, the granules, optionally with additional excipients, are compressed into tablets. The paroxetine tablets may be coated by a suitable film-coating, e.g., similar to the coating used in the commercially available tablets of paroxetine hydrochloride hemihydrate. Suitable techniques of coating include aqueous coating, non-aqueous coating or a melt coating process. Coating mixtures are commercially available. Coating for extended or delayed release of the active substance is also applicable to the composition of our invention. Coating mixtures may contain suitable colorants.

[0035] The paroxetine-containing granulate may also be used for preparation of capsulized unit dosage forms. The dry granulate may be optionally screened and/or pelletized

by methods known per se to obtain particulate material of uniform size and shape. The granules or pellets are then filled into suitable capsules made from e.g. gelatine, hydroxypropylmethyl cellulose or starch. Capsules having low moisture content are preferred. Coating of the produced granulate is normally not necessary.

[0036] Paroxetine-containing granulate may also be filled into sachets containing the required unit dose of paroxetine. Such sachets are administered by dispersing or dissolving the content thereof in a suitable liquid, e.g. in water, and drinking. The compositions may contain suitable taste-masking excipients, flavors or sweeteners.

[0037] Another suitable final form comprising granulates according to the present invention are effervescent tablets, granulates or powders. They are formed by mixing the granulate with a suitable effervescent system by methods known per se.

[0038] The compositions of the present invention can be made by any conventional process including dry process such as dry blending, dry granulation, and direct compression as well as by wet processes such as wet granulation. In some embodiments, especially for paroxetine sulfonate salts, it is preferable to use water in the aid of mixing. For example, a granulate is formed by combining a paroxetine sulfonate salt and at least one excipient and mixing them in the presence of added water, followed by drying to remove substantially all of the added water. The resulting population of granules, or the "granulate," is dried to have an average content of remaining "added water" of 2.0 wt % or less, preferably 1.3 wt % or less, more preferably 1.0 wt % or less and even 0.8 wt % or less, based on the total weight of the granulate.

[0039] Typically the water is added in one of two ways, although the invention is not limited thereto. In a first method, water is added to paroxetine sulfonate and an excipient. The amount of water added is normally between 5 and 25 wt %, more typically between 10 and 20 wt %, based on the total weight of the resulting wet mixture. More water can be added, i.e., 30 wt %, 40 wt % or even 50 wt %, but some difficulties may be encountered concerning possible modifications of the excipient (for instance microcrystalline cellulose may change crystal form) and additional energy will be needed to remove the higher amounts of added water. The paroxetine sulfonate salt and the excipient are normally in powder form and pre-mixed or blended to form a powder bed prior to the addition of water. Alternatively, the excipient can be in granulate form and admixed with the paroxetine sulfonate powder. The excipient is generally one or more diluents such as calcium phosphate, microcrystalline cellulose, or both.

[0040] The wet mixture is stirred, usually under vigorous conditions, to form a homogeneous mixture. The added water is removed from the wetted mixture normally as rapidly as possible. The added water can be removed by heating as well as by passing a nitrogen gas stream over (or through) the mixture, or a combination thereof. The use of a nitrogen gas stream is also advantageous in that the presence of oxygen is reduced or avoided. The drying of the added water can occur after, during or simultaneously with the mixing/stirring step. To reduce the chance of color formation, the average residence time of the added water in contact with the paroxetine sulfonate and excipient(s) during

US 2004/0067254 A1

Apr. 8, 2004

5

the mixing and drying steps is generally less than 3 hours, more typically less than 2 hours, more typically less than 1.5 hours, frequently less than or equal to 1 hour and is normally in the range of 30 to 90 minutes, more preferably 30 to 60 minutes, depending upon the apparatus volumes, etc. Upon completion of the stirring and drying steps, a paroxetine sulfonate-containing granulate is obtained having a low added water content as described above.

[0041] For preparation of a final mixture for compressing into a tablet core (pre-compression mixture), the above paroxetine sulfonate-containing granulate is optionally mixed with additional diluent(s), a disintegrant and/or a lubricant such as magnesium stearate, in a suitable mixer, e.g. in a free-fall mixer. The pre-compression mixture is finally compressed into tablets by a suitable tableting press under ordinary conditions. The other excipients for mixing with the granulate should also be chosen, in terms of kind and grade, such that the final pre-compressing mixture exhibits a pH value of 6.5 or less as described above.

[0042] A second method for forming the granulate involves combining the added water with the paroxetine sulfonate to form an aqueous solution of paroxetine sulfonate. This aqueous solution is then added to at least one excipient. As in the first method, the excipient can be in powder or granulate form. The aqueous solution is generally a concentrated solution having at least 10 wt % paroxetine sulfonate, preferably at least 30 wt %, and more preferably at least 40 wt % paroxetine sulfonate. By using a concentrated solution, less water is needed, thereby saving energy in the drying step and allowing for faster drying times. These highly concentrated solutions are possible because of the advantageous water solubility of paroxetine sulfonate in comparison to other paroxetine salts such as paroxetine hydrochloride. The stirring and drying steps as well as the work up of the granulate into a pre-compression composition are carried out as described above.

[0043] A preferred formulation made by this process comprises adding the concentrated paroxetine sulfonate aqueous solution to either calcium hydrogen phosphate or microcrystalline cellulose followed by stirring and drying to form a paroxetine-containing granulate. To the formed granulate is then mixed the other one of the calcium hydrogen phosphate or microcrystalline cellulose which was not used to form the granulate along with sodium starch glycolate (a disintegrant) and magnesium stearate. The resulting mixed composition is ready for compression into tablets. An example of this composition contains 7.24 wt % paroxetine sulfonate (as the equivalent free base), 57.76 wt % of  $\text{CaHPO}_4$ , 30.0 wt % microcrystalline cellulose (Avicel PH 101), 4.0 wt % sodium starch glycolate, and 1 wt % magnesium stearate.

[0044] In the aqueous granulation procedure for preparation of tablets or capsules of paroxetine mesylate, microcrystalline cellulose and various forms and grades of calcium phosphate, typically calcium hydrogen phosphate, are the preferred solid diluents. However, the composition of this invention and the process for its preparation is not limited thereto. Alternate diluents include mono- and di saccharide sugars such as lactose, mannitol, lactitol, xylitol or combinations thereof.

[0045] Alternatively, a dry process can also be carried out wherein the paroxetine salt is dry blended with an excipient,

typically a calcium phosphate or microcrystalline cellulose, or both and optionally with a disintegrant. After blending, the mixture is compressed into a tablet.

[0046] For both wet and dry processes, it is sometimes advantageous to provide multiple mixing steps to facilitate high quality, homogenous mixing. For example, a portion of the binder(s) and/or disintegrant(s) are mixed with the paroxetine salt, optionally with the aide of water as described above. To this mixture the remainder of the binder(s) and/or disintegrant(s) are mixed. To this resulting mixture the remaining excipients such as a lubricant(s) are mixed. Such partial mixing can use more steps or fewer steps and can split intermediate mixtures into portions to facilitate apparatus volumes. Additionally, excipients can be pre-treated by techniques known in the art as desired, including wet granulation and dry granulation treatments. The binders or fillers such as calcium phosphate anhydrate can be pretreated with water and dried (<0.5% water) before being combined with the paroxetine salt or solution.

[0047] The composition of the present invention can be used to treat or prevent the following disorders: depression, obsessive compulsive disorder, alcoholism, anxiety, panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia, pre-menstrual syndrome, adolescent depression, trichotillomania, dysthymia, substance abuse etc. Most suitably, the composition of the invention is applied for treatment of depression, obsessive compulsive disorder and panic disorder.

[0048] The treatment or prevention of any one or more of the above disorders is performed by administering orally the composition comprising an effective and/or prophylactic amount of the paroxetine sulfonate to a patient in need thereof. The patient can be a mammal including a human, a dog, a horse, or a monkey.

[0049] The composition of this invention is advantageously presented as a unit dose composition, preferably in a form of a tablet or a capsule, comprising paroxetine sulfonate equivalent to from 1 to 200 mg of paroxetine free base, more usually from 5 to 100 mg, for example from 10 to 50 mg. Typical tablet doses are 10, 20, 30, and 40 mg. Such a composition is normally taken by a human patient from 1 to 6 times daily, but more usually once or twice daily, with the total amount of paroxetine sulfonate administered being generally between 5 to 400 mg of paroxetine. A suitable daily dose is from 0.05 to 6 mg/kg, ore preferably 0.14 to 0.86 mg/kg.

## EXAMPLES

### Example 1

[0050] Granulate of Paroxetine Mesylate for Tablet Production

[0051] 1. Prepare a pre-blend of 3177.5 g of calcium hydrogen phosphate anhydrate (A-TAB pH 5.1) and 29.75 g of sodium starch glycolate by mixing for 5 minutes in a high-shear granulator.

[0052] 2. Prepare a solution of 258.3 g of paroxetine mesylate in 350 ml of water.

[0053] 3. Add the solution to the pre-blend granulate from the step 1 at ambient temperature.

US 2004/0067254 A1

Apr. 8, 2004

6

[0054] 4. Dry the wet granulate at 40° C. under diminished pressure and nitrogen flow to less than 1% water content.

[0055] 5. Mix the resulted granulate with 29.75 g of sodium starch glycollate for 15 minutes in a free-fall mixer; add 70.0 g of magnesium stearate to the mixture and mix for 5 minutes.

[0056] Tablet cores containing 40 mg of paroxetine are prepared from the resulting granulate (pH=5.53) on a suitable tableting machine (tablet weight 713 mg, punch diameter 10 mm, hardness 80 N). Despite the use of water to aid in the mixing, these tablets did not turn pink upon storage under accelerated conditions (40° C./75%RH) packaged in PVC/PE/PVDC—aluminium blisters or in HDPE containers.

#### Example 2

[0057] Granulate of Paroxetine Mesylate for Tablets

[0058] The process as in Example 1 was maintained with the modification that the steps 3 and 4 are performed simultaneously, at 40° C. The time necessary for adding the paroxetine mesylate aqueous solution is approx. 15 minutes; for drying approx. 45 minutes. The composition has a pH of 5.37.

#### Example 3

[0059]

Tablets of paroxetine mesylate are made having the following composition:				
Paroxetine mesylate	12.915 mg (10 mg equiv.)	25.83 mg (20 mg equiv.)	38.745 mg (30 mg equiv.)	51.66 mg (40 mg equiv.)
Calcium hydrogen phosphate anhydrate	158.88 mg	317.75 mg	476.64 mg	635.50 mg
pH 5.1				
Sodium starch glycollate	2.975 mg	5.95 mg	8.925 mg	11.90 mg
Magnesium stearate	3.50 mg	7.00 mg	10.50 mg	14.00 mg

[0060] The tablets are made as follows. Paroxetine mesylate is mixed with calcium hydrogen phosphate. 10% water is added and the mixture granulated and dried to an added water content of around 1%. The resulting granulate is mixed with the sodium starch glycollate, and magnesium stearate in a free fall mixer and compressed into tablets; each tablet having the above composition. The pH varies from 5.2 to 5.8 depending upon the batches of excipients used.

#### Example 4

[0061]

Tablets of Paroxetine mesylate	
Paroxetine mesylate	51.66 mg (equivalent to 40 mg of paroxetine free base)
Calcium hydrogen phosphate	411.83 mg
Microcrystalline cellulose	213.92 mg

-continued

Tablets of Paroxetine mesylate	
Sodium starch glycollate	28.52 mg
Magnesium stearate	7.13 mg

[0062] Tablets having the above composition are made as follows. Paroxetine mesylate is mixed with calcium hydrogen phosphate. 10% water is added and the mixture granulated and dried to an added water content of around 1%. The resulting granulate is mixed with microcrystalline cellulose, sodium starch glycollate, and magnesium stearate in a free fall mixer and compressed into tablets; each tablet having the above composition. The pH is 5.45.

#### Example 5

[0063] The same tablets as Example 4 are made, but first a paroxetine mesylate aqueous solution having a paroxetine mesylate concentration of about 30 wt % is formed. This solution is added to microcrystalline cellulose and dried to form a granulate. The produced granulate is mixed with calcium hydrogen phosphate, sodium starch glycollate, and magnesium stearate in a free fall mixer and compressed into tablets. The pH is 5.26.

#### Example 6

[0064]

Tablets of Paroxetine mesylate	
Composition per 1 g of tablet core:	
Paroxetine mesylate	72 mg
Mannitol	300 mg
Calcium hydrogen phosphate	533 mg
Croscarmellose sodium	20 mg
Povidone	30 mg
Magnesium stearate	15 mg

[0065] 1. Granulate 30% solution of paroxetine mesylate with a pre-blend mixture of mannitol, calcium hydrogen phosphate and croscarmellose sodium and dry to water content less than 1%.

US 2004/0067254 A1

Apr. 8, 2004

7

[0066] 2. Mix the dried and screened granulate with povidone and magnesium stearate. The granulate is suitable for compression into tablets containing 20 mg paroxetine.

## Example 7

[0067]

Tablets of Paroxetine mesylate	
Composition of 1 g of tablet core:	
Paroxetine mesylate	72 mg
Microcrystalline cellulose	290 mg
Calcium hydrogen phosphate	580 mg
Sodium starch glycolate	28 mg
Hydroxypropyl cellulose	20 mg
Magnesium stearate	10 mg

[0068] 1. Granulate 30% aqueous solution of paroxetine mesylate with a pre-blend mixture of microcrystalline cellulose, calcium hydrogen phosphate and sodium starch glycolate and dry.

[0069] 2. Mix the dried and screened granulate with hydroxypropyl cellulose and magnesium stearate.

[0070] The granulate is suitable for compression into tablets containing 20 mg paroxetine and having a pH of 5.14.

[0071] In the following Examples 8-19, the compositions listed are processed substantially as in Example 1, e.g. a granulate is prepared by using a concentrated aqueous solution of paroxetine mesylate and the dry paroxetine mesylate-containing granulate with water content less than 1% is mixed with the remaining excipients to prepare a bulk material for processing into the listed final forms by conventional methods.

## Example 8

[0072]

Composition of effervescent tablets (per 1 g)	
a) granulate	
Paroxetine mesylate	26 mg
Mannitol	166 mg
b) Effervescent system	
Sodium bicarbonate	378 mg
Citric acid anhydrous	400 mg
Saccharin sodium	9 mg
Aspartame	3 mg
Sodium chloride	1.5 mg
Sodium lauryl sulfate	0.05%
Flavour	16 mg

## Example 9

[0073]

Composition of effervescent tablets (per 1 g)	
a) granulate	
Paroxetine mesylate	26 mg
Isomaltose	203 mg
b) Effervescent system	
Sodium bicarbonate	336 mg
Citric acid	400 mg
Sodium chloride	1.5 mg
Neo-DHC	5 mg
Sodium lauryl sulfate	0.5 mg
Flavour	18 mg

## Example 10

[0074]

Composition of dispersible tablets (per 1 g)	
a) granulate	
Paroxetine mesylate	72 mg
Pregelatinized starch	380 mg
Microcrystalline cellulose	380 mg
Sodium starch glycolate	100 mg
b) Other excipients	
Hydroxypropyl cellulose	20 mg
Sodium saccharin	8 mg
Sodium stearyl fumarate	10 mg
Colloidal silicic acid	10 mg
Flavour	20 mg

## Example 11

[0075]

Composition of dispersible tablets (per 1 g)	
a) granulate	
Paroxetine mesylate	72 mg
Mannitol	500 mg
Microcrystalline cellulose	260 mg
Crosspovidone	100 mg
b) Other excipients	
Sodium saccharin	8 mg
Sodium stearyl fumarate	10 mg
Colloidal silicon dioxide	10 mg
Flavour	20 mg

US 2004/0067254 A1

Apr. 8, 2004

8

## Example 12

[0076]

Composition of sublingual tablets (per 1 g)	
<u>a) granulate</u>	
Paroxetine mesylate	72 mg
Sucrose	650 mg
Sorbitol	258 mg
<u>b) Other excipients</u>	
Sodium stearyl fumarate	20 mg

## Example 13

[0077]

Composition of sublingual tablets (per 1 g)	
<u>a) granulate</u>	
Paroxetine mesylate	72 mg
Mannitol	318 mg
Microcrystalline cellulose	600 mg
<u>b) Other excipients</u>	
Magnesium stearate	10 mg

## Example 14

[0078]

Composition of controlled release tablets with hydrophilic matrix (per 1 g)	
<u>a) granulate</u>	
Paroxetine mesylate	72 mg
Hydroxypropylmethyl cellulose	700 mg
Hydroxypropyl cellulose	168 mg
<u>b) other ingredients</u>	
Povidone	40 mg
Sodium stearyl fumarate	20 mg

## Example 15

[0079]

Composition of controlled release tablets with hydrophobic matrix (per 1 g)	
<u>a) granulate</u>	
Paroxetine mesylate	72 mg
Microcrystalline cellulose	520 mg
<u>b) other ingredients</u>	
Glyceryl behenate	200 mg
Glyceryl palmitostearate	200 mg
Sodium stearyl fumarate	8 mg

## Example 16

[0080]

Composition for immediate-release hard-shell capsules (per 1 g)	
<u>a) granulate</u>	
Paroxetine mesylate	72 mg
Maltodextrin	820 mg
Pregelatinized starch	80 mg
<u>b) other ingredients</u>	
croscopovidone	20 mg
colloidal silicone dioxide	8 mg

[0081] The produced granulate should be sieved and filled per 333 mg into Size 2 capsule.

## Example 17

[0082]

Composition for enteric-release hard-shell capsules (per 1 g)	
<u>a) granulate</u>	
Paroxetine mesylate	72 mg
Sucrose-starch non-pareil seeds	790 mg
Eudragit L 30 D 55	123.5 mg
<u>b) other ingredients</u>	
talc	7 mg
polyethylene glycol 6000	7 mg
silicone dioxide	0.5 mg

[0083] The produced granulate should be sieved and filled per 333 mg into Size 2 capsule.

## Example 18

[0084]

Composition for controlled release hard-shell capsules (per 1 g)	
<u>a) granulate</u>	
Paroxetine mesylate	72 mg
microcrystalline cellulose	850 mg
Ethylcellulose	60 mg
Hydroxypropylcellulose	18 mg
<u>b) other ingredients</u>	
none	

[0085] The produced granulate should be sieved and filled per 350 mg into Size 2 capsule.

US 2004/0067254 A1

Apr. 8, 2004

9

## Example 19

[0086]

Composition for oral sachets (per 1 g)	
<u>a) granulate</u>	
Paroxetine mesylate	5 mg
Sucrose	565 mg
Mannitol	377 mg
Povidone	28 mg
<u>b) other ingredients</u>	
saccharin sodium	10 mg
Flavour	15 mg

[0087] The invention having been described, it will be readily apparent to those skilled in the art that further changes and modifications in actual implementation of the concepts and embodiments described herein can easily be made or may be learned by practice of the invention, without departing from the spirit and scope of the invention as defined by the following claims.

We claim:

1. A solid paroxetine composition comprising a paroxetine salt and an excipient wherein said composition has a pH of 6.5 or less.
2. The composition according to claim 1, wherein said pH is within the range of about 4.5 to 6.5.
3. The composition according to claim 1, wherein said paroxetine salt is a paroxetine sulfonate salt or a paroxetine hydrochloride salt.
4. The composition according to claim 3, wherein said pH is less than 6.0.
5. The composition according to claim 3, wherein said pH is within the range of about 4.5 to 6.5.
6. The composition according to claim 5, wherein said paroxetine salt is paroxetine methane sulfonate or paroxetine hydrochloride.
7. The composition according to claim 6, wherein said paroxetine salt is paroxetine methane sulfonate.
8. The composition according to claim 1, wherein the excipient is acidic calcium phosphate.
9. The composition according to claim 1, wherein said composition is a tablet and said paroxetine salt is contained in a pharmaceutically effective amount and is selected from paroxetine sulfonate salts and paroxetine hydrochloride salts.
10. The composition according to claim 9, wherein said excipient is selected from the group consisting of a diluent, a binder, a disintegrant, a lubricant, a colorant, or a combination of two or more thereof.
11. The composition according to claim 10, which does not contain a hydrosoluble or hydrophilic diluent.
12. The composition according to claim 11, which does not contain a taste masking coating.
13. The composition according to claim 11, which comprises calcium phosphate, a lubricant and a disintegrant.
14. The composition according to claim 13, wherein said paroxetine salt is paroxetine methane sulfonate salt.
15. A paroxetine solid dosage form comprising a paroxetine sulfonate salt and having been made with the aid of water.

16. The dosage form according to claim 15, wherein said dosage form is a tablet or a capsule.

17. The dosage form according to claim 16, wherein said paroxetine sulfonate salt is paroxetine methane sulfonate.

18. The dosage form according to claim 15, wherein said paroxetine sulfonate salt was combined as an aqueous solution with at least one excipient in preparing said dosage form.

19. The dosage form according to claim 18, wherein said dosage form has a pH of 6.5 or less.

20. A granulate formed by mixing water, paroxetine sulfonate, and at least one excipient and drying the resulting mixture.

21. The granulate according to claim 20, wherein said mixing was accomplished by adding together an aqueous solution of said paroxetine sulfonate salt with said at least one excipient.

22. The granulate according to claim 21, wherein said aqueous solution of paroxetine sulfonate salt is a concentrated solution having at least about a 10 wt % concentration of paroxetine sulfonate.

23. The granulate according to claim 22, wherein said aqueous solution has a paroxetine sulfonate salt concentration of at least about 30 wt %.

24. The granulate according to claim 20, wherein said mixing and said drying are carried out simultaneously.

25. The granulate according to claim 21, wherein said aqueous solution of paroxetine sulfonate was added to a powdered or granulated blend of said at least one excipient.

26. The granulate according to claim 20, wherein said granulate has an average remaining added water content of about 2.0 wt % or less.

27. The granulate according to claim 26, wherein said granulate has an average remaining added water content of about 1.0 wt % or less.

28. The granulate according to claim 27, wherein said granulate has an average remaining added water content of about 0.8 wt % or less.

29. The granulate according to claim 20, wherein said granulate composition exhibits a pH value of 6.5 or less.

30. The granulate according to claim 29, wherein said granulate has a pH of about 6.0 or less.

31. The granulate according to claim 29, wherein said granulate has a pH within the range of 4.5 to 6.5.

32. The granulate according to claim 20, wherein said paroxetine sulfonate salt is paroxetine methane sulfonate.

33. A process, which comprises:

mixing an aqueous solution containing at least 10 wt % of a paroxetine sulfonate with at least one solid excipient; and

drying to form a granulate.

34. The process according to claim 33, wherein said drying step produces a granulate having a remaining added water content of about 2.0 wt % or less.

35. The process according to claim 34, wherein said drying step produces a granulate having a remaining added water content of about 1.3 wt % or less.

36. The process according to claim 35, wherein said drying step produces a granulate having a remaining added water content of about 1.0 wt % or less.

37. The process according to claim 36, wherein said drying step produces a granulate having a remaining added water content of about 0.8 wt % or less.

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Apr. 8, 2004

10

38. The process according to claim 33, wherein said aqueous solution concentration of said paroxetine sulfonate is at least 30 wt %.

39. The process according to claim 38, wherein said aqueous solution concentration of said paroxetine sulfonate is at least 40 wt %.

40. The process according to claim 33, wherein said mixing and drying steps are performed concurrently.

41. The process according to claim 33, wherein said solid excipient is a granulate.

42. The process according to claim 33, which further comprises optionally mixing additional excipients with said granulate and pressing said granulate composition into a tablet.

43. The process according to claim 42, which further comprises film coating said tablet.

44. The process according to claim 33, which further comprises filling said granulate into a capsule or sachet.

45. The process according to claim 33, which further comprises processing said granulate into effervescent tablets, sublingual tablets, controlled release tablets or delayed release tablets.

46. The process according to claim 33 wherein the excipients comprise at least one ingredient selected from the group consisting of binders, disintegrants, and fillers.

47. The process according to claim 46, wherein said granulate exhibits a pH value of 6.5 or less.

48. The process according to claim 47, wherein said granulate has a pH of about 6.0 or less.

49. The process according to claim 47, wherein said granulate has a pH of about 5.5 or less.

50. The process according to claim 33, wherein said paroxetine sulfonate is paroxetine methane sulfonate.

\* \* \* \* \*

# EXHIBIT 42

# GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

Ninth Edition

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# Contents

Contributors	xiii
Consultants to the Editors	xvii
Preface	xix
Preface to the First Edition	xxi

## SECTION I

### GENERAL PRINCIPLES 1

#### Introduction 1

*Leslie Z. Benet*

#### 1. Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, and Elimination 3

*Leslie Z. Benet, Deanna L. Kroetz, and Lewis B. Sheiner*

#### 2. Pharmacodynamics: Mechanisms of Drug Action and the Relationship Between Drug Concentration and Effect 29

*Elliott M. Ross*

#### 3. Principles of Therapeutics 43

*Alan S. Nies and Stephen P. Spielberg*

#### 4. Principles of Toxicology and Treatment of Poisoning 63

*Curtis D. Klaassen*

#### 5. Gene-Based Therapy 77

*Stephen L. Eck and James M. Wilson*

## SECTION II

### DRUGS ACTING AT SYNAPTIC AND NEUROEFFECTOR JUNCTIONAL SITES 103

#### 6. Neurotransmission: The Autonomic and Somatic Motor Nervous Systems 105

*Brian B. Hoffman, Robert J. Lefkowitz, and Palmer Taylor*

<b>7. Muscarinic Receptor Agonists and Antagonists</b>	<b>141</b>
<i>Joan Heller Brown and Palmer Taylor</i>	
<b>8. Anticholinesterase Agents</b>	<b>161</b>
<i>Palmer Taylor</i>	
<b>9. Agents Acting at the Neuromuscular Junction and Autonomic Ganglia</b>	<b>177</b>
<i>Palmer Taylor</i>	
<b>10. Catecholamines, Sympathomimetic Drugs, and Adrenergic Receptor Antagonists</b>	<b>199</b>
<i>Brian B. Hoffman and Robert J. Lefkowitz</i>	
<b>11. 5-Hydroxytryptamine (Serotonin) Receptor Agonists and Antagonists</b>	<b>249</b>
<i>Elaine Sanders-Bush and Steven E. Mayer</i>	

## S E C T I O N   I I I

<b>DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM</b>	<b>265</b>
<b>12. Neurotransmission and the Central Nervous System</b>	<b>267</b>
<i>Floyd E. Bloom</i>	
<b>13. History and Principles of Anesthesiology</b>	<b>295</b>
<i>Sean K. Kennedy and David E. Longnecker</i>	
<b>14. General Anesthetics</b>	<b>307</b>
<i>Bryan E. Marshall and David E. Longnecker</i>	
<b>15. Local Anesthetics</b>	<b>331</b>
<i>William A. Catterall and Kenneth Mackie</i>	
<b>16. Therapeutic Gases</b>	<b>349</b>
<i>Roderic G. Eckenhoff and David E. Longnecker</i>	
<b>17. Hypnotics and Sedatives; Ethanol</b>	<b>361</b>
<i>William R. Hobbs, Theodore W. Rall, and Todd A. Verdoorn</i>	
<b>18. Drugs and the Treatment of Psychiatric Disorders: Psychosis and Anxiety</b>	<b>399</b>
<i>Ross J. Baldessarini</i>	
<b>19. Drugs and the Treatment of Psychiatric Disorders: Depression and Mania</b>	<b>431</b>
<i>Ross J. Baldessarini</i>	
<b>20. Drugs Effective in the Therapy of the Epilepsies</b>	<b>461</b>
<i>James O. McNamara</i>	

<b>21. Drugs Effective in the Therapy of Migraine</b>	<b>487</b>
<i>Stephen J. Peroutka</i>	
<b>22. Treatment of Central Nervous System Degenerative Disorders</b>	<b>503</b>
<i>David G. Standaert and Anne B. Young</i>	
<b>23. Opioid Analgesics and Antagonists</b>	<b>521</b>
<i>Terry Reisine and Gavril Pasternak</i>	
<b>24. Drug Addiction and Drug Abuse</b>	<b>557</b>
<i>Charles P. O'Brien</i>	

## S E C T I O N I V

**AUTACOIDS; DRUG THERAPY OF INFLAMMATION** **579**

<b>Introduction</b>	<b>579</b>
<i>William E. Serafin and Kenneth S. Babe, Jr.</i>	
<b>25. Histamine, Bradykinin and Their Antagonists</b>	<b>581</b>
<i>Kenneth S. Babe, Jr., and William E. Serafin</i>	
<b>26. Lipid-Derived Autacoids: Eicosanoids and Platelet-Activating Factor</b>	<b>601</b>
<i>William B. Campbell and Perry V. Halushka</i>	
<b>27. Analgesic-Antipyretic and Antiinflammatory Agents and Drugs Employed in the Treatment of Gout</b>	<b>617</b>
<i>Paul A. Insel</i>	
<b>28. Drugs Used in the Treatment of Asthma</b>	<b>659</b>
<i>William E. Serafin</i>	

## S E C T I O N V

**DRUGS AFFECTING RENAL AND CARDIOVASCULAR FUNCTION** **683**

<b>29. Diuretics</b>	<b>685</b>
<i>Edwin K. Jackson</i>	
<b>30. Vasopressin and Other Agents Affecting the Renal Conservation of Water</b>	<b>715</b>
<i>Edwin K. Jackson</i>	
<b>31. Renin and Angiotensin</b>	<b>733</b>
<i>Edwin K. Jackson and James C. Garrison</i>	

<b>32. Drugs Used for the Treatment of Myocardial Ischemia</b>	<b>759</b>
<i>Rose Marie Robertson and David Robertson</i>	
<b>33. Antihypertensive Agents and the Drug Therapy of Hypertension</b>	<b>781</b>
<i>John A. Oates</i>	
<b>34. Pharmacological Treatment of Heart Failure</b>	<b>809</b>
<i>Ralph A. Kelly and Thomas W. Smith</i>	
<b>35. Antiarrhythmic Drugs</b>	<b>839</b>
<i>Dan M. Roden</i>	
<b>36. Drugs Used in the Treatment of Hyperlipoproteinemias</b>	<b>875</b>
<i>Joseph L. Witztum</i>	

## S E C T I O N   V I

**DRUGS AFFECTING GASTROINTESTINAL FUNCTION** **899**

<b>37. Agents for Control of Gastric Acidity and Treatment of Peptic Ulcers</b>	<b>901</b>
<i>Laurence L. Brunton</i>	
<b>38. Agents Affecting Gastrointestinal Water Flux and Motility; Emesis and Antiemetics; Bile Acids and Pancreatic Enzymes</b>	<b>917</b>
<i>Laurence L. Brunton</i>	

## S E C T I O N   V I I

**DRUGS AFFECTING UTERINE MOTILITY** **937**

<b>39. Agents That Cause Contraction or Relaxation of the Uterus</b>	<b>939</b>
<i>Cornelia R. Graves</i>	

## S E C T I O N   V I I I

**CHEMOTHERAPY OF PARASITIC INFECTIONS** **955**

<b>Introduction</b>	<b>955</b>
<i>James W. Tracy and Leslie T. Webster, Jr.</i>	
<b>40. Drugs Used in the Chemotherapy of Protozoal Infections: Malaria</b>	<b>965</b>
<i>James W. Tracy and Leslie T. Webster, Jr.</i>	

41. **Drugs Used in the Chemotherapy of Protozoal Infections: Trypanosomiasis, Leishmaniasis, Amebiasis, Giardiasis, Trichomoniasis, and Other Protozoal Infections** 987  
*James W. Tracy and Leslie T. Webster, Jr.*
42. **Drugs Used in the Chemotherapy of Helminthiasis** 1009  
*James W. Tracy and Leslie T. Webster, Jr.*

## S E C T I O N I X

**CHEMOTHERAPY OF MICROBIAL DISEASES** 1027

43. **Antimicrobial Agents: General Considerations** 1029  
*Henry F. Chambers and Merle A. Sande*
44. **Antimicrobial Agents: Sulfonamides, Trimethoprim-Sulfamethoxazole, Quinolones, and Agents for Urinary Tract Infections** 1057  
*Gerald L. Mandell and William A. Petri, Jr.*
45. **Antimicrobial Agents: Penicillins, Cephalosporins, and Other  $\beta$ -Lactam Antibiotics** 1073  
*Gerald L. Mandell and William A. Petri, Jr.*
46. **Antimicrobial Agents: The Aminoglycosides** 1103  
*Henry F. Chambers and Merle A. Sande*
47. **Antimicrobial Agents: Tetracyclines, Chloramphenicol, Erythromycin, and Miscellaneous Antibacterial Agents** 1123  
*Joan E. Kapusnik-Uner, Merle A. Sande, and Henry F. Chambers*
48. **Antimicrobial Agents: Drugs Used in the Chemotherapy of Tuberculosis and Leprosy** 1155  
*Gerald L. Mandell and William A. Petri, Jr.*
49. **Antimicrobial Agents: Antifungal Agents** 1175  
*John E. Bennett*
50. **Antimicrobial Agents: Antiviral Agents** 1191  
*Frederick G. Hayden*

## S E C T I O N X

**CHEMOTHERAPY OF NEOPLASTIC DISEASES** 1225

- Introduction** 1225  
*Paul Calabresi and Bruce A. Chabner*

x

## CONTENTS

- 51. Antineoplastic Agents** 1233  
*Bruce A. Chabner, Carmen J. Allegra, Gregory A. Curt,  
 and Paul Calabresi*

## S E C T I O N X I

**DRUGS USED FOR IMMUNOMODULATION** 1289

- 52. Immunomodulators: Immunosuppressive Agents and Immunostimulants** 1291  
*Robert B. Diasio and Albert F. LoBuglio*

## S E C T I O N X I I

**DRUGS ACTING ON THE BLOOD AND THE BLOOD-FORMING  
ORGANS** 1309

- 53. Hematopoietic Agents: Growth Factors, Minerals, and Vitamins** 1311  
*Robert S. Hillman*
- 54. Anticoagulant, Thrombolytic, and Antiplatelet Drugs** 1341  
*Philip W. Majerus, George J. Broze, Jr., Joseph P. Miletich, and Douglas M. Tollefsen*

## S E C T I O N X I I I

**HORMONES AND HORMONE ANTAGONISTS** 1361

- 55. Adenohypophyseal Hormones and Their Hypothalamic Releasing Factors** 1363  
*Mario Ascoli and Deborah L. Segaloff*
- 56. Thyroid and Antithyroid Drugs** 1383  
*Alan P. Farwell and Lewis E. Braverman*
- 57. Estrogens and Progestins** 1411  
*Cynthia L. Williams and George M. Stancel*
- 58. Androgens** 1441  
*Jean D. Wilson*
- 59. Adrenocorticotrophic Hormone; Adrenocortical Steroids and Their Synthetic  
 Analogs; Inhibitors of the Synthesis and Actions of Adrenocortical Hormones** 1459  
*Bernard P. Schimmer and Keith L. Parker*

- 60. Insulin, Oral Hypoglycemic Agents, and the Pharmacology of the Endocrine Pancreas** 1487  
*Stephen N. Davis and Daryl K. Granner*
- 61. Agents Affecting Calcification and Bone Turnover: Calcium, Phosphate, Parathyroid Hormone, Vitamin D, Calcitonin, and Other Compounds** 1519  
*Robert Marcus*

## S E C T I O N X I V

**THE VITAMINS** 1547

- Introduction** 1547  
*Robert Marcus and Ann M. Coulston*
- 62. Water-Soluble Vitamins: The Vitamin B Complex and Ascorbic Acid** 1555  
*Robert Marcus and Ann M. Coulston*
- 63. Fat-Soluble Vitamins: Vitamins A, K, and E** 1573  
*Robert Marcus and Ann M. Coulston*

## S E C T I O N X V

**DERMATOLOGY** 1591

- 64. Dermatological Pharmacology** 1593  
*Cynthia Guzzo, Gerald S. Lazarus, and Victoria P. Werth*

## S E C T I O N X V I

**OPHTHALMOLOGY** 1617

- 65. Ocular Pharmacology** 1619  
*Sayoko E. Moroi and Paul R. Lichter*

## S E C T I O N X V I I

**TOXICOLOGY** 1647

- 66. Heavy Metals and Heavy-Metal Antagonists** 1649  
*Curtis D. Klaassen*

<b>67. Nonmetallic Environmental Toxicants: Air Pollutants, Solvents, Vapors, and Pesticides</b>	<b>1673</b>
<i>Curtis D. Klaassen</i>	

A P P E N D I C E S

<b>I. Principles of Prescription Order Writing and Patient Compliance Instructions</b>	<b>1697</b>
<i>Leslie Z. Benet</i>	
<b>II. Design and Optimization of Dosage Regimens; Pharmacokinetic Data</b>	<b>1707</b>
<i>Leslie Z. Benet, Svein Øie, and Janice B. Schwartz</i>	
<b>Index</b>	<b>1793</b>

## PRINCIPLES OF THERAPEUTICS

Alan S. Nies and Stephen P. Spielberg

*The regulations governing the development of new drugs have evolved over the past century to assure the safety and efficacy of new medications for the population. The safety or efficacy of a drug in an individual patient is never assured. Because all patients differ in their responses to drugs, each therapeutic encounter must be considered an experiment with a hypothesis that can be tested. The scientific basis of the hypothesis derives from the database generated from controlled clinical trials during drug development and the experience obtained postmarketing. Well-defined endpoints must be established prior to therapy. These may be clinical endpoints, such as reduction of fever or pain, or they may be surrogate markers, such as reduction of blood cholesterol or blood pressure, that are correlated with the clinical outcome. Individualization of therapy for a particular patient requires a basic understanding of pharmacokinetics and pharmacodynamics. Many factors can influence that patient's response to a drug, including the age of the patient, disease of the organs of drug elimination (kidney, liver), the concurrent use of other drugs, foods, and chemicals (drug interactions), previous therapy with the same or similar drugs (tolerance), and a variety of genetic factors that can influence the kinetics and toxicity of drugs (pharmacogenetics). For a limited number of drugs, monitoring of the concentration of the drug in plasma can be useful to control for pharmacokinetic variability. Monitoring pharmacodynamic variability requires close attention to the patient's responses using predefined goals for acceptable efficacy and toxicity. Some adverse events are extensions of the drug's pharmacologic effect and often are avoidable if therapy is individualized. However, other serious adverse reactions are related to an interaction of the drug with variables unique to the individual patient. When a drug is first marketed, it has been tested in only a limited number of well-characterized patients. Adverse events that occur as commonly as 1/1000 patients may not be discovered prior to marketing, and rare events may not be discovered for several years after a drug is on the market. It is the responsibility of all health care professionals to monitor the effects of drugs postmarketing and to report serious adverse events that may be drug-related to the FDA and/or the drug manufacturer. In the future, it is likely that the genetic and environmental bases of rare, adverse drug reactions can be discovered and screening techniques applied to assess individual risk. This would improve the overall safety of pharmacotherapy.*

## THERAPY AS A SCIENCE

Over a century ago, Claude Bernard formalized criteria for gathering valid information in experimental medicine. However, application of these criteria to therapeutics and to the process of making decisions about therapeutics has, until recently, been slow and inconsistent. Although the diagnostic aspects of medicine are approached with scientific sophistication, therapeutic decisions often are made on the basis of impressions and traditions. Over the past

three decades, the principles of human experimentation have been defined, and the techniques for evaluation of therapeutic interventions have progressed to the point that it should now be considered absolutely unethical to apply the *art*, as opposed to the *science*, of therapeutics to any patient who directly (the adult or child) or indirectly (the fetus) receives drugs for therapeutic purposes. Therapeutics must now be dominated by objective evaluation of an adequate base of factual knowledge.

**Conceptual Barriers to Therapeutics as a Science.**

The most important barrier that inhibited the development of therapeutics as a science seems to have been the belief that multiple variables in diseases and in the effects of drugs are uncontrollable. If this were true, the scientific method would not be applicable to the study of pharmacotherapy. In fact, therapeutics is the aspect of patient care that is most amenable to the acquisition of useful data, since it involves an intervention and provides an opportunity to observe a response. It is now appreciated that clinical phenomena can be defined, described, and quantified with some precision. The approach to complex clinical data has been artfully discussed by Feinstein (1983).

Another barrier to the realization of therapeutics as a science was overreliance on traditional diagnostic labels for disease. This encouraged the physician to think of a disease as static rather than dynamic, to view patients with the same "label" as a homogeneous rather than a heterogeneous population, and to consider a disease as a single entity even when information about pathogenesis was not available. If diseases are not considered to be dynamic, "standard" therapies in "standard" doses will be the order of the day; decisions will be reflexive. Needed instead is an attitude that makes the physician responsible for recognition of and compensation for changes that occur in pathophysiology as the underlying process evolves. For example, the term *myocardial infarction* refers to localized destruction of myocardial cells caused by interruption of the blood supply; however, decisions about therapy must take into account a variety of autonomic, hemodynamic, and electrophysiological variables that change as a function of the time, size, and location of the infarction. Failure to take all such variables into account while planning a therapeutic maneuver may result in ineffective therapy in some patients while exposing others to avoidable toxicity. A diagnosis or label of a disease or syndrome usually indicates a spectrum of possible causes and outcomes. Therapeutic experiments that fail to control for the known variables that affect prognosis yield uninterpretable data.

A third conceptual barrier was the incorrect notion that data derived empirically are useless, because they are not generated by application of the scientific method. Empiricism often is defined as the practice of medicine founded on mere experience, without the aid of science or a knowledge of principles. The connotations of this definition are misleading; empirical observations need not be scientifically unsound. In fact, concepts of therapeutics have been greatly advanced by the clinical observer who makes careful and controlled observations on the outcome of a therapeutic intervention. The results, even when the mechanisms of disease and their interactions with the ef-

fects of drugs are not understood, are nevertheless often crucial to appropriate therapeutic decisions. Frequently, the initial suggestion that a drug may be efficacious in one condition arises from careful, empirical observations that are made while the drug is being used for another purpose. Examples of valid empirical observations that have resulted in new uses of drugs include the use of penicillamine to treat arthritis, lidocaine to treat cardiac arrhythmias, and propranolol and clonidine to treat hypertension. Conversely, empiricism, when not coupled with appropriate observational methods and statistical techniques, often results in findings that are invalid or misleading.

**Clinical Trials.** Application of the scientific method to experimental therapeutics is exemplified by a well-designed and well-executed clinical trial. Clinical trials form the basis for therapeutic decisions by all physicians, and it is therefore essential that they be able to evaluate the results and conclusions of such trials critically. To maximize the likelihood that useful information will result from the experiment, the objectives of the study must be defined, homogeneous populations of patients must be selected, appropriate control groups must be found, meaningful and sensitive indices of drug effects must be chosen for observation, and the observations must be converted into data and then into valid conclusions. The *sine qua non* of any clinical trial is its controls. Many different types of controls may be used, and the term *controlled clinical trial* is not synonymous with *randomized double-blind technique*. Selection of a proper control group is as critical to the eventual utility of an experiment as the selection of the experimental group. Although the randomized, double-blind controlled trial is the most effective design for avoiding bias and distributing unknown variables between the "treatment" and the "control" groups, it is not necessarily the optimal design for all studies. It may be impossible to use this design to study disorders that occur rarely, disorders in patients who cannot, by regulation or ethics or both, be studied (e.g., children, fetuses, or some patients with psychiatric diseases), or disorders with a typically fatal outcome (e.g., rabies), where historical controls can be used.

There are several requirements in the design of clinical trials to test the relative effects of alternative therapies. (1) *Specific outcomes* of therapy that are clinically relevant and quantifiable must be measured. These may include subjective assessments, which are important in determining whether a therapy improves the patient's well-being. Quality of life can be assessed by the experimental subject and can be tabulated objectively and incorporated into evaluation of a therapy (Guyatt *et al.*, 1993). Wherever possible, well-defined clinical endpoints, *i.e.*, survival or pain relief, should be used rather than an intermediate endpoint or "surrogate" marker (Temple, 1993; Nowak, 1994). A surrogate marker is a clinical or laboratory test that

correlates with the clinical outcome of a disease. Blood pressure, blood cholesterol, CD4 lymphocyte count in acquired immunodeficiency syndrome (AIDS), and premature ventricular complexes are examples of surrogate markers that have been used as endpoints in clinical trials. Although surrogate markers often are useful to reduce the length and sample size of a clinical trial, the results of such trials may be misleading, as the Cardiac Arrhythmia Suppression Trial (CAST) demonstrated (Echt *et al.*, 1991). In CAST, the antiarrhythmic drugs encainide, flecainide, and moricizine were effective in suppressing ventricular arrhythmias (the surrogate marker) in patients following a myocardial infarction, but the drugs, nonetheless, increased mortality. The ultimate test of a drug's efficacy must rest with actual clinical outcomes. (2) *The accuracy of diagnosis and the severity of the disease* must be comparable in the groups being contrasted; otherwise, false-positive and false-negative errors may occur. (3) *The dosages* of the drugs must be chosen and individualized in a manner that allows relative efficacy to be compared at equivalent toxicities or allows relative toxicities to be compared at equivalent efficacies. (4) *Placebo effects*, which occur in a large percentage of patients, can confound many studies—particularly those that involve subjective responses; controls must take this into account. (5) *Compliance* with the experimental regimens should be assessed before subjects are assigned to experimental or control groups. The drug-taking behavior of the subjects should be reassessed during the course of the trial. Noncompliance, even if randomly distributed between both groups, may cause falsely low estimates of the true potential benefits or toxicity of a particular treatment. (6) *Sample size* should be estimated prior to beginning a clinical trial to determine the power of the trial to detect a statistically significant effect if, in fact, such an effect exists. Depending upon such factors as the overall prognosis and variability of the disease and the anticipated improvement and variability in outcome or toxicity from the new treatment, very large numbers of subjects may be needed; otherwise, the possibility of a false-negative result is high (*i.e.*, no statistically significant differences between the two treatments will be found, even though differences actually exist). (7) *Ethical considerations* may be major determinants of the types of controls that can be used and must be evaluated explicitly (Passamani, 1991). For example, in therapeutic trials that involve life-threatening diseases for which there already is an effective therapy, the use of a placebo is unethical, and new treatments must be compared with "standard" therapies (Byar *et al.*, 1990).

The results of clinical trials of new therapeutic agents or of old agents for new indications may have severe limitations in terms of what can be expected of drugs when they are used in an office practice (Feinstein, 1994). The selection of patients for experimental trials usually eliminates those with coexisting diseases, and such trials usually assess the effect of only one or two drugs, not the many that might be given to or taken by the same patient under the care of a physician. Clinical trials usually are performed with relatively small numbers of patients for periods of time that may be shorter than are necessary in practice, and compliance may be better controlled than it can be in practice. These factors lead to several inescapable conclusions:

1. Even if the result of a valid clinical trial of a drug is thoroughly understood, the physician can only develop

a hypothesis about what the drug might do to any particular patient. In effect, the physician uses the results of a clinical trial to establish an experiment in each patient. The detection of anticipated and unanticipated effects and the determination of whether or not they are due to the drug(s) being used are important responsibilities of the physician during the supervision of a therapeutic regimen. If an effect of a drug is not seen in a clinical trial, it may still be revealed in the setting of clinical practice. About one-half or more of both useful and adverse effects of drugs that were not recognized in the initial formal trials subsequently were discovered and reported by practicing physicians.

2. If an anticipated effect of a drug has not occurred in a patient, this does not mean that the effect cannot occur in that patient or in others. Many factors in the individual patient may contribute to lack of efficacy of a drug. They include, for example, misdiagnosis, poor compliance by the patient to the regimen, poor choice of dosage or dosage intervals, coincidental development of an undiagnosed separate illness that influences the outcome, the use of other agents that interact with primary drugs to nullify or alter their effects, undetected genetic or environmental variables that modify the disease or the pharmacological actions of the drug, or unknown therapy by another physician who is caring for the same patient. Of equal importance, even when a regimen appears to be efficacious and innocuous, a physician should not attribute all improvement to the therapeutic regimen chosen, nor should a physician assume that a deteriorating condition reflects only the natural course of the disease. Similarly, if an anticipated untoward or toxic effect is not seen in a particular patient, it still can occur in others. Physicians who use only their own experience with a drug to make decisions about its use expose their patients unduly to unjustifiable risk. For example, simply because a doctor has not seen a case of chloramphenicol-induced aplastic anemia in practice does not mean that such a disaster may not occur; the drug still should be used for the proper indications.

3. Rational therapy is therapy based on observations that have been evaluated critically. It is no less crucial to have a scientific approach to the treatment of an individual patient than to use this approach when investigating drugs in a research setting. In both instances, it is the patient who benefits. Such an approach can be formalized in the practice setting by performing a randomized, controlled trial in an individual patient who has stable clinical symptomatology. With this strategy a specific therapy of uncertain efficacy can be com-

pared with a placebo or alternative therapy in a double-blind design with well-defined endpoints that are tailored to the individual patient. The outcome of such an "n of 1" trial is immediately relevant to the particular patient, although it may not apply to all other patients (Guyatt *et al.*, 1986).

## INDIVIDUALIZATION OF DRUG THERAPY

As has been implied above, therapy as a science does not apply simply to the evaluation and testing of new, investigational drugs in animals and human beings. It applies with equal importance to the treatment of each patient as an individual. Therapists of every type have long recognized and acknowledged that individual patients show wide variability in response to the same drug or treatment method. Progress has been made in identifying the sources of variability. Important factors are presented in Figure 3-1; the basic principles that underlie these sources of variability have been presented in Chapters 1 and 2. The following discussion relates to the strategies that have been developed to deal with variability in the clinical setting. (See also Appendix II.)

### Pharmacokinetic Considerations

Inpatient and outpatient variation in disposition of a drug must be taken into account in choosing a drug regimen. For a given drug, there may be wide variation in its pharmacokinetic properties among individuals. For some drugs, this variability may account for one-half or more of

the total variation in eventual response. The relative importance of the many factors that contribute to these differences depends in part on the drug itself and on its usual route of elimination. Drugs that are excreted primarily unchanged by the kidney tend to have smaller differences in disposition among patients with similar renal function than do drugs that are inactivated by metabolism. Of drugs that are extensively metabolized, those with high metabolic clearance and large first-pass elimination have marked differences in bioavailability, whereas those with slower biotransformation tend to have the largest variation in elimination rates among individuals. Studies in identical and nonidentical twins have revealed that genotype is a very important determinant of differences in the rates of metabolism (Penno and Vesell, 1983). For many drugs, physiological and pathological variations in organ function are major determinants of their rate of disposition. For example, the clearance of digoxin and gentamicin is related to the rate of glomerular filtration, whereas that of lidocaine and propranolol is dependent primarily on the rate of hepatic blood flow. The effect of diseases that involve the kidneys or liver is to impair elimination and to increase the variability in the disposition of drugs. In such settings, measurements of concentrations of drugs in biological fluids can be used to assist in the individualization of drug therapy. Since old age and renal or hepatic diseases also may affect the responsiveness of target tissues (*e.g.*, the brain), the physician should be alert to the possibility of a shift in the range of therapeutic concentrations.

A test should not be performed simply because an assay is available. More assays of drugs are available than are generally useful. Determinations of concentrations of drug in blood, serum, or plasma are particularly useful when well-defined criteria are fulfilled. (1) There must be a demonstrated relationship between the concentration of the drug in plasma and the eventual therapeutic effect that is desired and/or the toxic effect that must be avoided. (2) There should be substantial interpatient variability in disposition of the drug (and small inpatient variation). Otherwise, concentrations of drug in plasma could be predicted adequately from dose alone. (3) It should be difficult to monitor intended or unintended effects of the drug. Whenever clinical effects or minor toxicity are measured easily (*e.g.*, the effect of a drug on blood pressure), such assessments should be preferred in the decision to make any necessary adjustment of dosage of the drug. However, the effects of some drugs in certain settings are not easily monitored. For example, the effect of  $\text{Li}^+$  on manic-depressive psychosis may be delayed and difficult to quantify. For some drugs, the initial manifestation of toxicity may be serious (*e.g.*, digitalis-induced arrhythmias or theo-

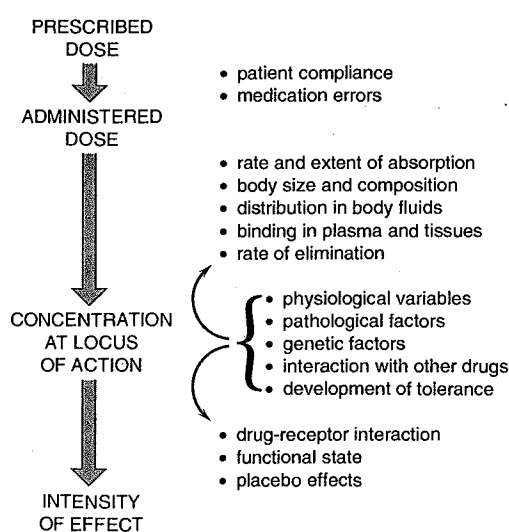


Figure 3-1. Factors that determine the relationship between prescribed drug dosage and drug effect. (Modified from Koch Weser, 1972.)

phylline-induced seizures). The same concepts apply to a number of agents used for cancer chemotherapy. Other drugs (*e.g.*, antiarrhythmic agents) produce toxic effects that mimic symptoms or signs of the disease being treated. Many drugs are used for prophylaxis of an intermittent, potentially dangerous event; examples include anticonvulsants and antiarrhythmic agents. In each of these situations, titration of drug dosage may be aided by measurements of concentrations of the drug in blood. (4) The concentration of drug required to produce therapeutic effects should be close to the value that causes substantial toxicity (*see below*). If this circumstance does not apply, patients could simply be given the largest dose known to be necessary to treat a disorder, as is commonly done with penicillin. However, if there is an overlap in the concentration-response relationship for desirable and undesirable effects of the drug, as is true for theophylline, determinations of concentration of drug in plasma may allow the dose to be optimized. All four of the above-described criteria should be met if the measurement of drug concentrations is to be of significant value in the adjustment of dosage. Knowledge of concentrations of drugs in plasma or urine also is particularly useful for detection of therapeutic failures that are due to lack of patient compliance with a medical regimen or for identification of patients with unexpected extremes in the rate of drug disposition.

Assay of drugs to assist the physician in achieving a desired concentration of drug in blood or plasma (*i.e.*, "targeting" the dose) is another example of the use of an intermediate or surrogate endpoint of therapy in place of the ultimate clinical goal. Surrogate markers also can be applied in other ways; one is to provide an indication for a change in the choice of drug therapy. Measurements of concentrations of drugs in plasma and/or measurements of one or more pharmacological effects of the drug can provide an indication of probable lack of efficacy. Other issues of importance with regard to the measurement and interpretation of drug concentrations are discussed in Chapter 1 and Appendix II.

### Pharmacodynamic Considerations

Considerable interindividual variation in the response to drugs remains after the concentration of the drug in plasma has been adjusted to a target value; for some drugs this pharmacodynamic variability accounts for much of the total variation in responsiveness among patients. As discussed in Chapter 2, the relationship among the concentration of a drug and the magnitude of the observed response may be complex, even when responses are mea-

sured in simplified systems *in vitro*, although typical sigmoidal concentration-effect curves usually are seen (*see Figure 2-5*). When drugs are administered to patients, however, there is no single characteristic relationship between the drug concentration in plasma and the measured effect; the concentration-effect curve may be concave upward, concave downward, linear, sigmoid, or inverted U-shaped. Moreover, the concentration-effect relationship may be distorted if the response being measured is a composite of several effects, such as the change in blood pressure produced by a combination of cardiac, vascular, and reflex effects. However, such a composite concentration-effect curve often can be resolved into simpler curves for each of its components. These simplified concentration-effect relationships, regardless of their exact shape, can be viewed as having four characteristic variables: potency, slope, maximal efficacy, and individual variation. These are illustrated in Figure 3-2 for the common sigmoid log dose-effect curve.

**Potency.** The location of the concentration-effect curve along the *concentration axis* is an expression of the potency of a drug. Although often related to the dose of a drug required to produce an effect, potency is more properly related to the concentration of the drug in plasma to approximate more closely the situation in isolated systems *in vitro* and to avoid the complicating factors of pharmacokinetic variables. Although potency obviously affects drug dosage, potency *per se* is relatively unimportant in the clinical use of drugs as long as the required dose can

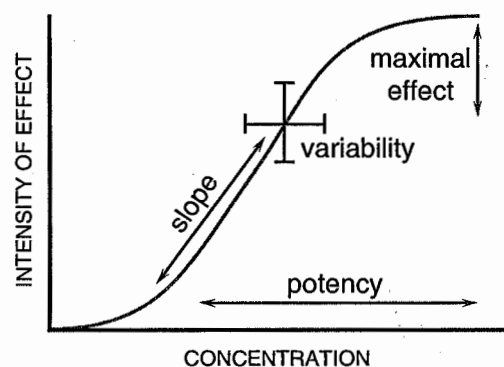


Figure 3-2. The log concentration-effect relationship.

Representative log concentration-effect curve, illustrating its four characterizing variables. Here, the effect is measured as a function of increasing drug concentration in the plasma. Similar relationships also can be plotted as a function of the dose of drug administered. These plots are referred to as dose-effect curves. *See text for further discussion.*

be given conveniently. There is no justification for the view that more potent drugs are superior therapeutic agents. However, if the drug is to be administered by transdermal absorption, a highly potent drug is required, since the capacity of the skin to absorb drugs is limited.

**Maximal Efficacy.** The maximal effect that can be produced by a drug is its *maximal*, or *clinical, efficacy* (which is related to, but not precisely the same as, the term *efficacy* as discussed in Chapter 2). Maximal efficacy is determined principally by the properties of the drug and its receptor-effector system and is reflected in the plateau of the concentration-effect curve. In clinical use, however, a drug's dosage may be limited by undesired effects, and the true maximal efficacy of the drug may not be achievable. The maximal efficacy of a drug is clearly a major characteristic—of much more clinical importance than is potency; furthermore, the two properties are not related and should not be confused. For instance, although some thiazide diuretics have similar or greater potency than the loop diuretic furosemide, the maximal efficacy of furosemide is considerably greater.

**Slope.** The slope of the concentration-effect curve reflects the mechanism of action of a drug, including the shape of the curve that describes drug binding to its receptor (see Chapter 2). The steepness of the curve dictates the range of doses that are useful for achieving a clinical effect. Aside from this fact, the slope of the concentration-effect curve has more theoretical than practical usefulness.

**Biological Variability.** Different individuals vary in the magnitude of their response to the same concentration of a single drug or to similar drugs when the appropriate correction has been made for differences in potency, maximal efficacy, and slope. In fact, a single individual may not always respond in the same way to the same concentration of drug. A concentration-effect curve applies only to a single individual at one time or to an average individual. The intersecting brackets in Figure 3-2 indicate that an effect of varying intensity will occur in different individuals at a specified concentration of a drug or that a range of concentrations is required to produce an effect of specified intensity in all of the patients.

Attempts have been made to define and measure individual "sensitivity" to drugs in the clinical setting, and progress has been made in understanding some of the determinants of sensitivity to drugs that act at specific receptors. For example, responsiveness to  $\beta$ -adrenergic receptor agonists may change because of disease (e.g.,

thyrotoxicosis or heart failure) or because of prior administration of either  $\beta$ -adrenergic agonists or antagonists that can cause changes in the concentration of the  $\beta$ -adrenergic receptor and/or coupling of the receptor to its effector systems (Caron and Leftkowitz, 1993; Carpena *et al.*, 1993; Collins *et al.*, 1992). Receptors are not static components of the cell; they are in a dynamic state that is influenced by both endogenous and exogenous factors.

**Concentration-Percent or Quantal Concentration-Effect Curve.** The concentration of a drug that produces a specified effect in a single patient is termed the *individual effective concentration*. This is a *quantal* response, since the defined effect is either present or absent. Individual effective concentrations usually are lognormally distributed, which means that a normal variation curve is the result of plotting the logarithms of the concentration against the frequency of patients achieving the defined effect (Figure 3-3, A). A cumulative frequency distribution of individuals achieving the defined effect as a function of drug concentration is the *concentration-percent curve* or the *quantal concentration-effect curve*. This curve resembles the sigmoid shape of the graded concentration-effect curve discussed above (Figure 3-2), but the slope of the concentration-percent curve is an expression of the pharmacodynamic variability in the population rather than an expression of the concentration range from a threshold to a maximal effect in the individual patient.

The dose of a drug required to produce a specified effect in 50% of the population is the *median effective dose*, abbreviated as the  $ED_{50}$  (Figure 3-3, B). In preclinical studies of drugs, the *median lethal dose*, as determined in experimental animals, is abbreviated as  $LD_{50}$ . The ratio of the  $LD_{50}$  to the  $ED_{50}$  is an indication of the *therapeutic index*, which is a statement of how *selective* the drug is in producing its desired effects. In clinical studies, the dose, or preferably the concentration, of a drug required to produce toxic effects can be compared to the concentration required for the therapeutic effects in the population to evaluate the clinical therapeutic index. However, since pharmacodynamic variation in the population may be marked, the concentration or dose of drug required to produce a therapeutic effect in most of the population will usually overlap the concentration required to produce toxicity in some of the population, even though the drug's therapeutic index may be large. Also, the concentration-percent curves for efficacy and toxicity need not be parallel, adding yet another complexity to the determination of the therapeutic index in patients. Finally, *no drug produces a single effect*, and, depending on the effect being measured, the therapeutic index for a drug will vary. For example, much less codeine is required for cough sup-

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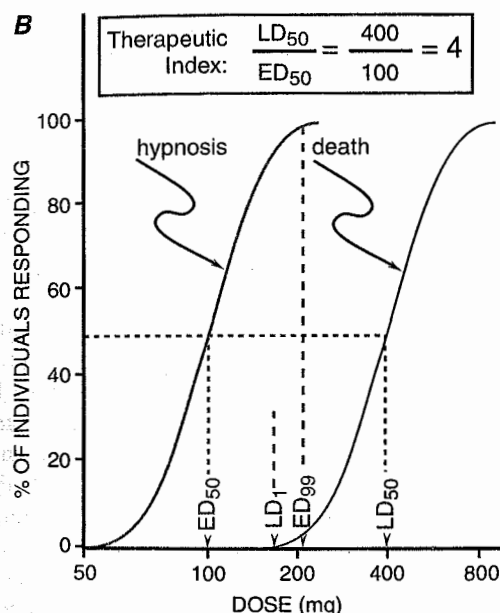
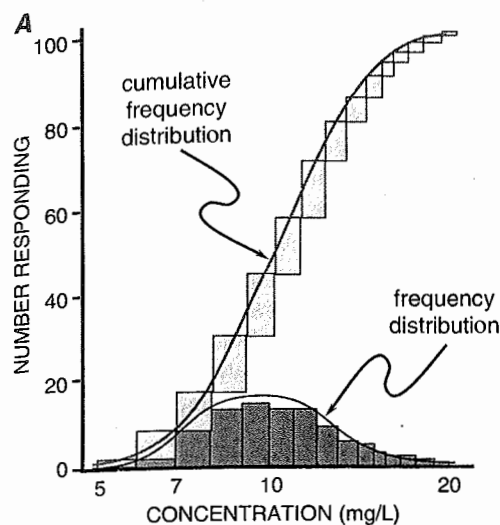


Figure 3-3. Frequency distribution curves and quantal concentration-effect and dose-effect curves.

**A. Frequency Distribution Curves.** An experiment was performed on 100 subjects, and the effective plasma concentration that produced a quantal response was determined for each individual. The number of subjects who required each dose is plotted, giving a lognormal frequency distribution (colored bars). The gray bars demonstrate that the normal frequency distribution, when summated, yields the cumulative frequency distribution—a sigmoidal curve that is a quantal concentration-effect curve. **B. Quantal Dose-Effect Curves.** Animals were injected with varying doses of sedative-hypnotic, and the responses determined and plotted. The calculation of the therapeutic index, the ratio of the LD<sub>50</sub> to the ED<sub>50</sub>, is an indication of how selective a drug is in producing its desired effects relative to its toxicity. (See text for additional explanation).

pression than for control of pain in 50% of the population, and thus the margin of safety, selectivity, or therapeutic index of codeine is much greater as an antitussive than as an analgesic.

### Other Factors That Affect Therapeutic Outcome

The variation in pharmacokinetic and pharmacodynamic parameters that accounts for much of the need to individualize therapy has been discussed. Other factors, listed in Figure 3-1, also should be considered as potential determinants of success or failure of therapy. The following presentation serves as an introduction to these subjects, some of which also are discussed in Chapter 1 and Appendix II.

**Age.** Most drugs are developed and tested in young to middle-aged adults. At each extreme of the age spectrum individuals differ both in the way they handle drugs (pharmacokinetics) and in their response to drugs (pharmacodynamics). These differences may require substantial alterations in the dose or dose regimen to produce the desired effect in the young or in the very old.

**Children.** Most medications are not developed or specifically evaluated in children, and formulations often are inadequate for proper administration. Thus, development of new drugs for children, and rational use of old compounds, requires an integrated approach to pharmacokinetic, pharmacodynamic, and formulation issues. There is no reliable, broadly applicable principle or formula for converting doses of drugs used in adults to doses that are safe and effective in children. When the drug manufacturer does not provide adequate information about pediatric dosage, there can be substantial risk in deriving a dose for children and infants from an adult dose by, for example, simply reducing the dose based upon body weight or surface area. In general, pathways of drug clearance (hepatic and renal) are limited in the newborn, particularly the premature infant. The unique physiology of the newborn has led to past therapeutic disasters such as gray baby syndrome (inadequate glucuronidation of chloramphenicol with drug accumulation) and sulfonamide-induced kernicterus (displacement of bilirubin from plasma proteins in the face of increased bilirubin productions from fetal erythrocyte turnover, decreased bilirubin conjugation, acidosis, and decreased blood-brain barrier). Careful pharmacokinetic studies in the newborn coupled with clinical therapeutic drug monitoring have markedly improved our knowledge of neonatal developmental pharmacology and resulted in safe therapeutics.

Pathways of drug clearance develop variably over the first year of life, and may be influenced by induction of drug metabolizing enzymes (*e.g.*, phenobarbital exposure). Precise developmental patterns have not been mapped out for most isoforms of cytochrome P450. For CYP1A2, studies using caffeine as a model substrate have revealed the pattern shown in Figure 3-4 (Lambert *et al.*, 1986). Such a pattern has been noted for many compounds (theophylline, anticonvulsants) where a very limited metabolic clearance in the newborn matures during the first year of life (albeit with considerable intersubject and metabolic pathway variability) and ultimately achieves weight-adjusted clearance values that exceed those of adults. At puberty, clearance begins to decline, earlier in girls than in boys, to adult levels. The mechanisms regulating such developmental changes are uncertain, and other pathways of drug clearance likely mature with different patterns. The critical point is that, at times of physiologic change (the premature, the neonate, puberty), major changes in pharmacokinetics are likely to occur, variability is likely to be the greatest (both within the same patient over time and among patients), and dosing adjustment, often aided by therapeutic drug monitoring for drugs with narrow therapeutic indices, becomes critical to safe, effective therapeutics. The 7-day-old neonate may be very different pharmacokinetically from the same patient as a newborn, and doses that were appropriate for a 10-year-old on a weight-adjusted basis might well result in overdose for the same patient at age 14.

Pharmacodynamic differences between children and adults have led to unexpected outcomes of therapy and adverse effects. For example, while antihistamines and barbiturates generally sedate adults, these drugs cause many children to become "hyperactive." Of great concern are the effects of medications, particularly when used chronically, on physical and cognitive development. Chronic therapy

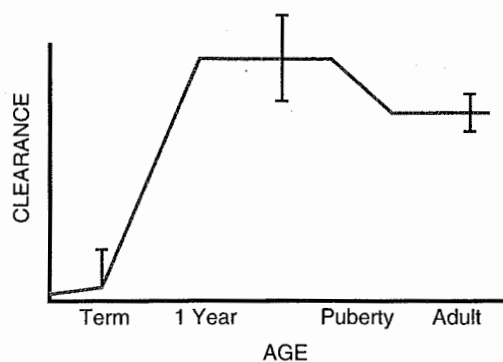


Figure 3-4. Representative developmental changes in drug clearance.

with phenobarbital can have a significant effect on learning and behavior in children. Tetracyclines deposit in developing teeth with resultant permanent staining. While children are at risk for all the side effects of chronic corticosteroid therapy seen in adults, such drugs will also stunt linear growth. Children, however, are not always at increased risk for adverse drug effects. For example, while young children appear to be at higher risk for hepatotoxicity from valproic acid than adults, they are at much lower risk for hepatotoxicity from isoniazid.

Pediatric formulations of old and new drugs remain a problem for practical therapeutics. While toxicity of the vehicles used to administer drugs led to the Pure Food and Drug Act of 1938 (diethylene glycol toxicity from elixir of sulfanilamide), as recently as the 1980s, the "gasping syndrome" associated with excess administration of drugs preserved with benzylalcohol was described in the newborn. For intravenous medications, formulations are often too concentrated for proper measurement of tiny doses required for newborns. Oral formulations frequently present major problems with palatability and possible adverse reactions to flavoring and coloring agents. Particularly for pediatric suspensions, syrups, and chewable tablets, different preparations of the same drugs, while being equivalent from the point of view of bioavailability, may differ in acceptability to a specific patient.

**The Elderly.** As adults age, gradual changes in drug kinetics and effects result in an increase in the interindividual variability of doses required for a given effect. The pharmacokinetic changes result from changes in body composition and the function of drug-eliminating organs. The reduction in lean body mass, serum albumin, and total body water and the increase in percentage of body fat result in changes in distribution of drugs depending on their lipid solubility and protein binding. The clearance of many drugs is reduced in the elderly. Renal function declines at a variable rate to about 50% of that in the young adult. Hepatic blood flow and the function of some of the drug-metabolizing enzymes also is reduced in the elderly, but the variability of this change is great. In general, the activities of cytochrome P450 enzymes are reduced, but conjugation mechanisms are relatively well maintained. Frequently, the elimination half-life of drugs is increased as a consequence of a larger apparent volume of distribution (of lipid soluble drugs) and/or a reduction of the renal or metabolic clearance.

Changes in pharmacodynamics also are important factors in treating the elderly. Drugs that depress the central nervous system produce increased effects at any given plasma concentration. Physiologic changes and loss of homeostatic resilience can result in increased sensitivity to

unwanted effects of drugs, such as hypotension from psychotropic medications and hemorrhage from anticoagulants, even if dosage is appropriately adjusted to account for the age-related pharmacokinetic changes.

The proportion of our population in the elderly and very old age groups is increasing. These individuals have more illnesses than younger people and consume a disproportionate share of prescription and over-the-counter drugs. These factors, combined with the changes in pharmacokinetics and pharmacodynamics that occur with aging, make the elderly age group a population in whom drug use is likely to be marred by serious adverse drug effects and drug interactions. It is a population that should receive drugs only when absolutely necessary for well-defined indications and at the lowest effective doses. Prospectively defined endpoints, appropriate use of therapeutic drug monitoring, and frequent reviews of the patient's drug history with discontinuation of those drugs that did not achieve the endpoint desired or are no longer required would greatly improve the health of the elderly population.

**Drug-Drug Interactions.** The use of several drugs often is essential to obtain a desired therapeutic objective or to treat coexisting diseases. Examples abound, and the choice of drugs to be employed concurrently can be based on sound pharmacological principles. In the treatment of hypertension, a single drug is effective in only a modest percentage of patients. In the treatment of heart failure, the concurrent use of a diuretic with a vasodilator and/or a cardiac glycoside often is essential to achieve an adequate cardiac output and to keep the patient free from edema. Multiple-drug therapy is the norm in cancer chemotherapy and for the treatment of certain infectious diseases. The goals in these cases usually are to improve therapeutic effectiveness and to delay the emergence of malignant cells or of microorganisms that are resistant to the effects of available drugs. When physicians use several drugs concurrently, they face the problem of knowing whether a specific combination in a given patient has the potential to result in an interaction, and, if so, how to take advantage of the interaction if it leads to improvement in therapy or how to avoid the consequences of an interaction if they are adverse.

A *potential drug interaction* refers to the possibility that one drug may alter the intensity of pharmacological effects of another drug given concurrently. The net result may be enhanced or diminished effects of one or both of the drugs or the appearance of a new effect that is not seen with either drug alone.

The frequency of significant beneficial or adverse drug interactions is unknown. Surveys that include data ob-

tained *in vitro*, in animals, and in case reports tend to predict a frequency of interactions that is higher than actually occurs. While such reports have contributed to skepticism about the overall importance of drug interactions, there are potential interactions of definite clinical importance, and the physician must be alert to the possibility of their occurrence. Estimates of the incidence of clinical drug-drug interactions range from 3 to 5% in patients taking a few drugs to 20% in patients who are receiving 10 to 20 drugs. Because most hospitalized patients receive at least six drugs, the scope of the problem clearly is significant. Recognition of beneficial effects and recognition and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed, an inclination to attribute unusual events to drugs rather than to disease, and adequate observation of the patient. Automated monitoring of prescription orders in the hospital or outpatient pharmacy may decrease the physician's need to memorize potential interactions. Nevertheless, knowledge of likely mechanisms of drug interactions is the only way the clinician can be prepared to analyze new findings systematically. It is incumbent upon the physician to be familiar with the basic principles of drug-drug interactions in planning a therapeutic regimen. Such reactions are discussed for individual drugs throughout this textbook.

Interactions may be either pharmacokinetic (alteration of the absorption, distribution, or elimination of one drug by another) or pharmacodynamic (*e.g.*, interactions between agonists and antagonists at drug receptors). The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences. Additionally, drug-drug interactions can be clinically important if the disease being controlled with the drug is serious or potentially fatal if undertreated.

**Pharmacokinetic Drug-Drug Interactions.** Drugs may interact at any point during their absorption, distribution, metabolism, or excretion; the result may be an increase or decrease in the concentration of drug at the site of action. As individuals vary in their rates of disposition of any given drug, the magnitude of an interaction that alters pharmacokinetic parameters is not always predictable but can be very significant.

The delivery of drug into the circulation may be altered by physicochemical interactions that occur prior to absorption. For example, drugs may interact in an intravenous solution to produce an insoluble precipitate that may or may not be obvious. In the gut, drugs may chelate with metal ions or adsorb to medicinal resins. Thus,  $\text{Ca}^{2+}$  and other metallic cations contained in antacids are chelated

by tetracycline, and the complex is not absorbed. Cholestyramine adsorbs and inhibits the absorption of thyroxine, cardiac glycosides, warfarin, corticosteroids, and probably other drugs. The rate and sometimes the extent of absorption can be affected by drugs that alter gastric motility, but this is usually of little clinical consequence. Interactions within the gut may be indirect and complex. Antibiotics that alter the gastrointestinal flora can reduce the rate of bacterial synthesis of vitamin K such that the effect of oral anticoagulants, which compete with vitamin K, will be enhanced. If a drug is metabolized by the gastrointestinal microorganisms, antibiotic therapy may result in an increase in the absorption of the drug, as has been demonstrated for some patients receiving digoxin (Lindenbaum *et al.*, 1981).

Many drugs are extensively bound to plasma albumin (acidic drugs) or  $\alpha_1$ -acid glycoprotein (basic drugs). In general, only unbound drug is free to exert an effect or to be distributed to the tissues. Thus, displacement of one drug from its binding site by another might be expected to result in a change in drug effects. Although such binding/displacement interactions occur, they are rarely of clinical significance. This is because the displaced drug distributes rapidly into the tissues; the larger the apparent volume of distribution of the drug, the less is the rise in the concentration of free drug in the plasma. Furthermore, following the displacement, more free drug is available for metabolism and excretion. Thus, the body's clearance processes eventually reduce the free drug concentration to that which existed prior to the drug displacement interaction. As a result, the effect of such an interaction is usually small, transient, and frequently unrecognized. However, the relationship of free drug to the total (bound plus free) drug is changed, and the interpretation of plasma drug assays that measure total drug concentration must be altered.

A few drugs are actively transported to their site of action. For instance, the antihypertensive drugs, guanethidine and guanadrel, cause inhibition of sympathetic nervous system function after being transported into adrenergic neurons by the norepinephrine uptake mechanism. Inhibition of this neuronal uptake system by tricyclic antidepressants and some sympathomimetic amines will inhibit the sympathetic blockade and reduce the antihypertensive effects of guanethidine and guanadrel.

Interactions involving drug metabolism can increase or decrease the amount of drug available for action by inhibition or induction of metabolism, respectively (*see also* Chapter 1). Interactions may occur among administered drugs, or between drugs and dietary substances (*e.g.*, naringenin in grapefruit juice [a CYP3A4 inhibitor]) or other chemicals (*e.g.*, alcohol and other organic solvents [CYP2E1 inducers]; cigarette smoke, polychlorinated biphenyls [CYP1A2 inducers]). The effects of enzyme induction or inhibition are most obvious when drugs are given orally, because all of the absorbed compound must pass through the liver prior to reaching the systemic circulation. Therefore, even for drugs that have a systemic clearance that is mainly dependent on hepatic blood flow (*e.g.*, propranolol), the amount of drug that escapes metabolism on the first pass will be influenced by enzyme induction or inhibition. Examples of drugs that are affected by enzyme inducers are oral anticoagulants, quinidine, corticosteroids, low-dose estrogen contraceptives, theophylline, mexiletine, methadone, and some  $\beta$ -adrenergic blocking agents. Knowledge of the specific pathways of metabolism of a drug, and of the molecular mechanisms of enzyme induction, can help in planning studies of possible drug interactions. Thus, if a compound is found to be metabolized by CYP3A4 in *in vitro* studies, the potential for clinically significant interactions can be focused on studies with commonly used drugs that can either inhibit (*e.g.*, ketoconazole) or in-

duce (*e.g.*, rifampin) this enzyme. The recent example of arrhythmias triggered by a combination of terfenadine and ketoconazole highlights the need for such studies. In this interaction, ketoconazole inhibits the metabolism of terfenadine (by CYP3A4) to its active metabolite, resulting in high concentrations of unmetabolized terfenadine, which is toxic (Peck *et al.*, 1993).

The ability of one drug to inhibit the renal excretion of another is dependent on an interaction at active transport sites. Many of the reported interactions occur at the anion transport site, where, for example, probenecid inhibits the excretion of penicillin to cause the desirable effects of elevated plasma concentrations of the antibiotic and a longer half-life. Similarly, the renal elimination of methotrexate is inhibited by probenecid, salicylates, and phenylbutazone, but in this case methotrexate toxicity may result from the interaction. Interactions at the transport site for basic drugs include the inhibition of excretion of procainamide by cimetidine and amiodarone. An interaction at an unknown tubular site causes inhibition of the excretion of digoxin by quinidine, verapamil, and amiodarone. Finally, the excretion of  $\text{Li}^+$  can be affected by drugs that alter the ability of the proximal renal tubule to reabsorb  $\text{Na}^+$ . Thus, clearance of  $\text{Li}^+$  is reduced and concentrations of  $\text{Li}^+$  in plasma are increased by diuretics that cause volume depletion and by nonsteroidal antiinflammatory drugs that enhance proximal tubular reabsorption of  $\text{Na}^+$ .

**Pharmacodynamic Drug-Drug Interactions.** There are numerous examples of drugs that interact at a common receptor site or that have additive or inhibitory effects due to actions at different sites in an organ. Such interactions are described throughout this textbook. Frequently overlooked is the multiplicity of effects of many drugs. Thus, phenothiazines are effective  $\alpha$ -adrenergic antagonists; many antihistamines and tricyclic antidepressants are potent antagonists at muscarinic receptors. These "minor" actions of drugs may be the cause of drug interactions.

Other interactions of an apparently pharmacodynamic nature are poorly understood or are mediated indirectly. Halogenated hydrocarbons, including many general anesthetics, sensitize the myocardium to the arrhythmogenic actions of catecholamines. This effect may result from an action on the pathway that leads from adrenergic receptor to effector, but the details are unclear. The striking interaction between meperidine and monoamine oxidase inhibitors to produce seizures and hyperpyrexia may be related to excessive amounts of an excitatory neurotransmitter, but the mechanism has not been elucidated.

One drug may alter the normal internal milieu, thereby augmenting or diminishing the effect of another agent. A well-known example of such an interaction is the enhancement of the toxic effects of digoxin as a result of diuretic-induced hypokalemia.

**Summary: Drug-Drug Interactions.** Drug-drug interactions are only one of the many factors discussed in this chapter that can alter the patient's response to therapy. The major task of the physician is to determine if an interaction has occurred and the magnitude of its effect. When unexpected effects are seen, a drug interaction should be

suspected. Careful drug histories are important, because patients may take over-the-counter drugs, may take drugs prescribed by another physician, or may take drugs prescribed for another patient. Care must be exercised when major changes are made in a drug regimen, and drugs that are not necessary should be discontinued. When an interaction is discovered, the interacting drugs often may be used effectively with adjustment of dosage or other therapeutic modifications.

**Fixed-Dose Combinations.** The concomitant use of two or more drugs adds to the complexity of individualization of drug therapy. The dose of each drug should be adjusted to achieve optimal benefit. Thus, patient compliance is essential, yet more difficult to achieve. To obviate the latter problem, many fixed-dose drug combinations are marketed. The use of such combinations is advantageous only if the ratio of the fixed doses corresponds to the needs of the individual patient.

In the United States, a fixed-dose combination of drugs is considered a "new drug" and as such must be approved by the Food and Drug Administration (FDA) before it can be marketed, even though the individual drugs are available for concurrent use. To be approved, certain conditions must be met. The two drugs must act to achieve a better therapeutic response than either drug alone (e.g., many antihypertensive drug combinations); or one drug must act to reduce the incidence of adverse effects caused by the other (e.g., a diuretic that promotes the urinary excretion of  $K^+$  combined with a  $K^+$ -sparing diuretic).

**Placebo Effects.** The net effect of drug therapy is the sum of the pharmacological effects of the drug and the nonspecific placebo effects associated with the therapeutic effort. Although identified specifically with administration of an inert substance in the guise of medication, placebo effects are associated with the taking of any drug, active as well as inert.

Placebo effects result from the physician-patient relationship, the significance of the therapeutic effort to the patient, and the mental set imparted by the therapeutic setting and by the physician. They vary significantly in different individuals and in any one patient at different times. Placebo effects are commonly manifested as alterations of mood, other subjective effects, and objective effects that are under autonomic or voluntary control. They may be favorable or unfavorable relative to the therapeutic objectives. Exploited to advantage, placebo effects can significantly supplement pharmacological effects and can represent the difference between success and failure of therapy.

A placebo (in this context, better termed *dummy medication*) is an indispensable element of the controlled clinical trial. In contrast, a placebo has only a limited role in the routine practice of medicine. A supportive physician-patient relationship generally is preferable to the use of a placebo for promoting therapeutic benefits. Relief or lack of relief of symptoms upon administration of a placebo is not a reliable basis for determining whether the symptoms have a "psychogenic" or "somatic" origin.

**Tolerance.** Tolerance may be acquired to the effects of many drugs, especially the opioids, various central nervous system (CNS) depressants, and organic nitrates. When this occurs, *cross-tolerance* may develop to the effects of pharmacologically related drugs, particularly those acting at the same receptor site, and drug dosage must be increased to maintain a given therapeutic effect. Since tolerance does not usually develop equally to all effects of a drug, the therapeutic index may decrease. However, there also are examples of the development of tolerance to the undesired effects of a drug and a resultant increase in its therapeutic index (e.g., tolerance to sedation produced by phenobarbital when used as an anticonvulsant).

The mechanisms involved in the development of tolerance are only partially understood. In animals, tolerance often occurs as the result of induced synthesis of the hepatic microsomal enzymes involved in drug biotransformation; the possible significance of this *drug-disposition* or *pharmacokinetic tolerance* during chronic medication in human beings is an area of continuing investigation. The most important factor in the development of tolerance to the opioids, barbiturates, ethanol, and organic nitrates is some type of cellular adaptation referred to as *pharmacodynamic tolerance*; multiple mechanisms are involved. Tachyphylaxis, such as that to histamine-releasing agents and to the sympathomimetic amines that act indirectly by releasing norepinephrine, has been attributed to depletion of available mediator, but other mechanisms also may contribute. The subject of tolerance is discussed in more detail in Chapter 24.

**Genetic Factors.** Genetic factors are the major determinants of the normal variability of drug effects and are responsible for a number of striking quantitative and qualitative differences in pharmacological activity. Basic principles of human genetics apply to genetic loci coding for proteins involved in handling of drugs, e.g., drug metabolizing enzymes, carrier proteins, and receptors. Thus (1) allelic variation is common; (2) there are often several different alleles producing variant proteins at a given locus; (3) some allelic variants are "silent" with no functional consequences, while others may markedly alter the handling of foreign compounds; (4) gene frequencies for

different alleles are likely to vary among different human populations, suggesting the need for vigilance in extrapolation of kinetic and safety data from one population to another; (5) some allelic variants are classified as "polymorphisms," variant alleles with a frequency of at least 1%, while other less common variants are classified as "rare in-born errors of metabolism." The consequences of pharmacogenetic variation include: (1) altered clearance of drugs resulting in a "functional overdose" in those individuals unable to metabolize the compound; (2) failure to convert a pro-drug to an active drug; (3) altered pharmacodynamics (e.g., hemolytic anemia secondary to glucose-6-phosphate dehydrogenase deficiency); and (4) idiosyncratic drug reactions such as aplastic anemia or hepatotoxicity.

The superfamily of cytochrome P450 enzymes has been extensively investigated for pharmacogenetic variants (Nelson *et al.*, 1993). For example, an abnormality in CYP2D6 (present in 3% to 10% of various populations) results in deficient metabolism of many compounds. For some of these drugs, for example the tricyclic antidepressants, toxicity of "standard" doses may result from accumulation when used in CYP2D6-deficient patients, while for other drugs, either because of wide therapeutic index (e.g., dextromethorphan) or because multiple pathways are involved in clearance (e.g., propranolol), no dosage adjustment is required.

During drug development, compounds may be screened *in vitro* with human tissue preparations or recombinantly expressed human cytochrome P450 enzymes to ascertain if pharmacogenetic polymorphisms are likely to be involved in metabolism of the drug. Single-dose studies in subjects genotyped for various polymorphisms may help clarify whether the potential for altered drug handling is clinically relevant. For pharmacogenetics to become clinically useful, molecular diagnostic tests for pharmacogenetic variants, done in routine clinical laboratories, must become available so that a physician can individualize choice of medication or dose regimen based on that specific patient's drug metabolism profile. If a relatively rare but severe adverse reaction to a drug (e.g., a 1/5000 risk of hepatotoxicity) is strongly linked to a given pharmacogenetic polymorphism, such pharmacogenetic "pre-screens" could markedly decrease the risk for individual patients and the population as a whole.

### Approach To Individualization

After it has been determined that pharmacotherapy is necessary to modify the symptoms or outcome of a disease, the therapist is faced with two types of decisions: the first is qualitative (the initial choice of a specific drug) and the second is quantitative (the initial dosage regimen). Optimal treatment will result only when the physician is aware of the sources of variation in response to drugs and when the dosage regimen is designed on the basis of the best available data about the diagnosis, severity and stage of the disease, presence of concurrent diseases or drug treatment, and predefined goals of acceptable efficacy and limits of acceptable toxicity. If objectively assessable expectations

of drug therapy are not set before therapy is initiated, therapy is likely to be ineffective and continued longer than necessary, unless an obvious adverse effect occurs.

In most clinical settings, the decision about the choice of drug is influenced substantially by the confidence the physician has in the accuracy of the diagnosis and estimates of the extent and severity of disease. Based on the best available information, the physician must decide on an initial drug from a group of reasonable alternatives. The extent of this evaluation is itself dependent on many factors, including a cost-benefit analysis of diagnostic tests, and this must be based on the availability and specificity of alternative therapies, and the likelihood of a reduction in future utilization of expensive health care. The initial dosage regimen is determined by estimation, if possible, of the pharmacokinetic properties of the drug in the individual patient. The estimate must be based on an appreciation of the variables that are most likely to affect the disposition of the particular drug. These variables have been discussed above (*see* Figure 3-1 and Appendix II). Subsequent adjustments may be aided in some instances by measurement of drug concentrations but must ultimately be based on whether the regimen is efficacious, either without adverse effects or at an acceptable level of toxicity.

It has been stated above that every therapeutic plan is and should be treated as an experiment. As such, most of the considerations that were specified in the discussion of clinical trials must be applied to individual patients. Of utmost importance is the definition of specific goals of treatment and the means to assess whether these goals are being achieved. Whenever possible, the objective endpoint should be related as closely as possible to the clinical goals of therapy (e.g., shrinkage of a tumor or eradication of an infection). Many clinical goals are, however, difficult to assess (e.g., the prevention of cardiovascular complications associated with hypertension and diabetes). In such cases, it is necessary to use surrogate markers, such as a reduction in blood pressure or the concentration of glucose or cholesterol in plasma. These intermediate endpoints are based on demonstrated (in clinical trials) or assumed correlation of the surrogate marker with the ultimate clinical benefit. In many cases, such as reduction of the concentration of cholesterol in plasma by drugs, the elimination of asymptomatic ventricular arrhythmias, or the change in CD4 lymphocyte count in AIDS, the link between the surrogate marker and the ultimate goal is controversial.

The value or utility of each regimen needs to be assessed at intervals during the course of therapy. The utility of a regimen can be defined as the benefit it produces plus the dangers of not treating the disease minus the sum of the adverse effects of therapy. Another common ex-

pression of the usefulness of a regimen is its ratio of risks to benefits (representing a balance between the efficacious and toxic effects of the drug). A definitive evaluation of the utility of a drug is not easy; nevertheless, some sense of the value of a regimen must be established in the minds of the physician and the patient. Knowledge of the usefulness of a given regimen may be a critical determinant of protracted compliance by the patient to a long-term regimen or logical discontinuation by the physician of a marginally efficacious and risky therapy. It must be remembered that the physician, the patient, and the patient's family may have disparate opinions of the utility of a therapeutic regimen. In one study of antihypertensive therapy where all patients were judged to be improved by the physician, only 48% of the patients considered themselves improved and 8% felt worse. Relatives thought that only 1% of the patients were improved and that 99% had evidence of adverse effects of therapy (Jachuck *et al.*, 1982).

### DRUG REGULATION AND DEVELOPMENT

**Drug Regulation.** The history of drug regulation in the United States reflects the growing involvement of governments in most countries to ensure some degree of efficacy and safety in marketed medicinal agents. The first act, the Federal Food and Drug Act of 1906, was concerned with the interstate transport of adulterated or misbranded foods and drugs. There were no obligations to establish drug efficacy and safety. The federal act was amended in 1938, following the deaths of about 100 children that resulted from the marketing of a solution of sulfanilamide in diethylene glycol, an excellent but highly toxic solvent. The amended act, the enforcement of which was entrusted to the FDA, was concerned primarily with the truthful labeling and safety of drugs. Toxicity studies were required, as well as approval of a new drug application (NDA), before a drug could be promoted and distributed. However, no proof of efficacy was required, and extravagant claims for therapeutic indications were commonly made. Drugs could go from the laboratory to clinical testing without approval by the FDA.

In this relatively relaxed atmosphere, research in basic and clinical pharmacology burgeoned in both industrial and academic laboratories. The result was a flow of new drugs, called "wonder drugs" by the lay press, for the treatment of both infectious and organic disease. Because efficacy was not rigorously defined, a number of therapeutic claims could not be supported by data. The risk-to-benefit ratio was seldom mentioned, but it emerged in dramatic fashion early in the 1960s. At that time thalidomide, a hypnotic with no obvious advantage over other drugs in its class, was introduced in Europe. After a short period, it became apparent that the incidence of a relatively rare birth defect, phocomelia, was increasing. It soon reached epidemic proportions, and retrospective epidemiological research firmly established the causative agent to be thalidomide taken early in the course of pregnancy. The reaction to the dramatic demonstration of the teratogenicity of a needless drug was worldwide. In the United States, it resulted in the Harris-Kefauver Amendments to the Food, Drug, and Cosmetic Act in 1962.

The Harris-Kefauver Amendments are sound legislation. They require sufficient pharmacological and toxicological research in animals before a drug can be tested in human beings. The data from such studies must be submitted to the FDA in the form of an application for an investigational new drug (IND) before clinical studies can begin. Three phases of clinical testing (*see below*) have evolved to provide the data that are used to support a new drug application. For drugs introduced after 1962, proof of efficacy is required, as is documentation of relative safety in terms of the risk-to-benefit ratio for the disease entity to be treated. The 1962 amendments also required manufacturers to provide data to support the claims of efficacy for all drugs marketed between 1938 and 1962.

The provisions of the Harris-Kefauver amendments have greatly increased the time and the cost required to market a new drug. Moreover, although the law requires action on the part of the FDA within a period of 6 months, an NDA may be returned to the applicant for additional basic or clinical research, so that the period actually required for approval of an NDA is on the order of 2 to 3 years. The total time of drug development from the time of filing of an IND application to final approval averages 8 to 9 years (Dimasi *et al.*, 1994). The result has been an increase in the inherent tension that exists between the FDA, which is motivated to protect the public health, and the drug developers, who are motivated to market effective and profitable drug products. Additionally, medical practitioners have criticized the FDA for delaying the approval of new drugs, whereas some consumer groups demand the recall of drugs that may play an important part in the therapeutic regimen of appropriately selected patients. In this climate, the FDA has the difficult task of balancing the requirement to ensure the safety of new drugs with the needs of society for useful medications to be made available in a timely manner. This dilemma has been brought into sharp focus recently by the demands of patients with AIDS for new and effective therapies. In response to the needs of patients with AIDS and other life-threatening illnesses, the FDA is moving on several fronts (Young *et al.*, 1988). First, the FDA has initiated new "treatment" IND regulations that allow patients with life-threatening diseases for which there is no satisfactory alternative treatment to receive drugs for therapy prior to general marketing if there is limited evidence of drug efficacy without unreasonable toxicity (Figure 3-5). Second, the agency has established a priority system to expedite reviews for drugs used to treat life-threatening diseases. Congress has enacted a "Drug User Fee", whereby the FDA collects a fee from drug manufacturers that is to be used to help fund the personnel required to speed the review process. Finally, the FDA is becoming involved more actively in drug development to facilitate the approval of drugs designed to treat life-threatening and severely debilitating diseases. By working with the pharmaceutical industry throughout the period of clinical drug development, the FDA hopes to reduce the time from submission of an IND application to the approval of an NDA. This streamlining process will be accomplished by the interactive design of well-planned, focused clinical studies using validated surrogate markers or clinical endpoints other than survival or irreversible morbidity. Sufficient data then should be available earlier in the development process to allow a risk-benefit analysis and a possible decision for approval. In some cases, this system may reduce or obviate the need for phase 3 testing prior to approval. Coupled with this expedited development process will be the requirement, when appropriate, for restricted distribution to certain specialists or facilities and for postmarketing studies to answer remaining issues of risks, benefits, and optimal uses of the drug. If postmarketing studies are inadequate or demonstrate lack of safety or clinical benefit,

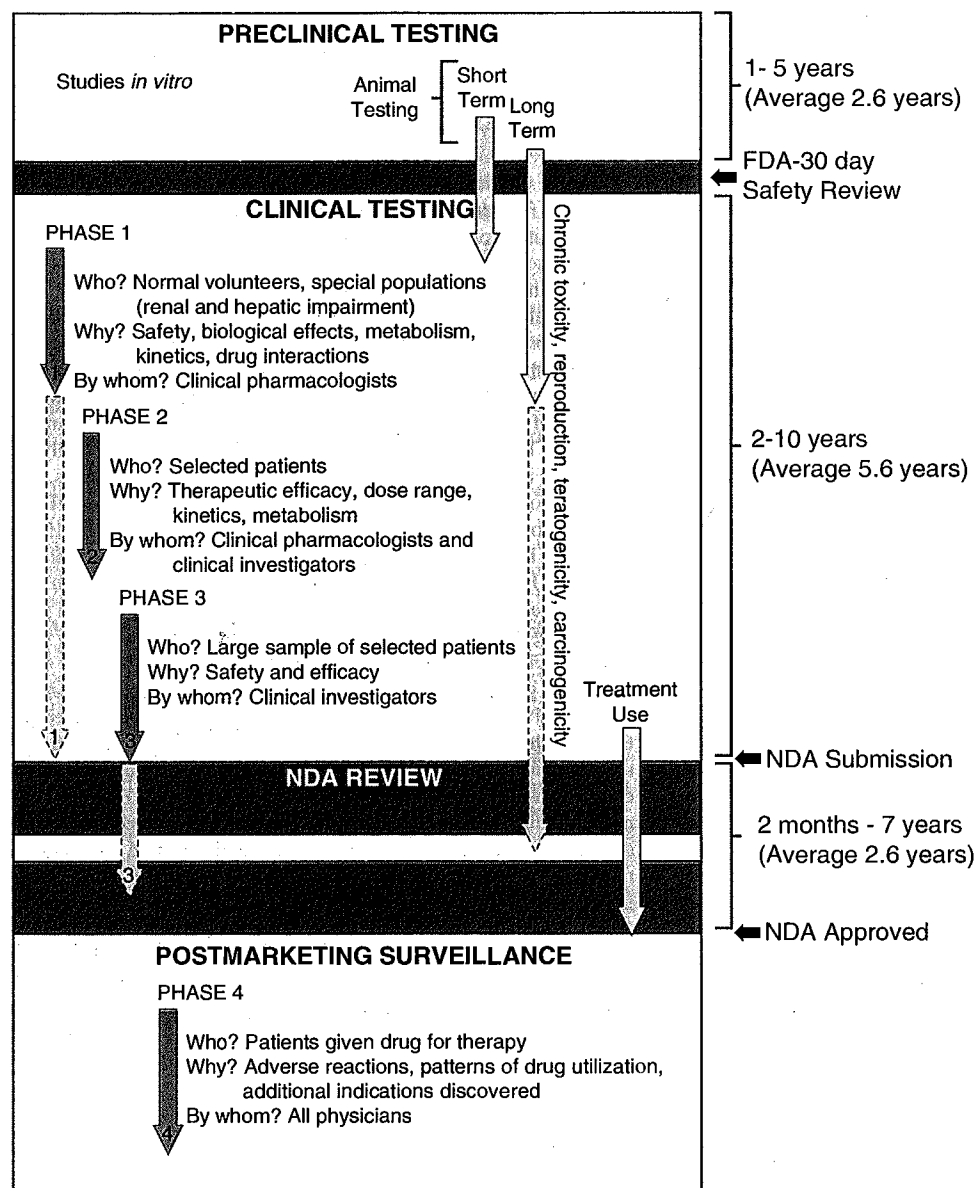


Figure 3-5. The phases of drug development in the United States. (See Smith, 1978; Kaitlin *et al.*, 1987; and Young *et al.*, 1988.)

approval for the new drug may be withdrawn (21 C.F.R. §§314.510 through 314.530). This new initiative by the FDA is based on the assumption that society is willing to accept unknown risks from drugs used to treat life-threatening or debilitating diseases. Some worry that such shortcuts in the drug approval process will result in the release of drugs without sufficient information to determine their utility and proper use (Stolley, 1993). However, as long as the patient's safety can be reasonably ensured, the new plans to accelerate the drug-development process should prove beneficial to patients with such illnesses.

A seemingly contradictory directive to the FDA also is contained in the Food, Drug, and Cosmetic Act—that is, the FDA cannot in-

terfere with the practice of medicine. Thus, once the efficacy of a new agent has been proven in the context of acceptable toxicity, the drug can be marketed. The physician then is allowed to determine its most appropriate use. However, physicians must realize that new drugs are inherently more risky because of the relatively small amount of data about their effects. Yet, there is no practical way to increase knowledge about a drug before it is marketed. A systematic method for postmarketing surveillance is an indispensable requirement for early optimization of drug use.

Before a drug can be marketed, a package insert for use by physicians must be prepared. This is a cooperative effort between the FDA and the pharmaceutical company. The insert usually contains basic

pharmacological information, as well as essential clinical information in regard to approved indications, contraindications, precautions, warnings, adverse reactions, usual dosage, and available preparations. Promotional materials cannot deviate from information contained in the insert.

**Drug Development.** Except for concern about the so-called drug lag (Kaitin *et al.*, 1994) and governmental interference with the practice of medicine, the average physician has not considered it important to understand the process of drug development. Yet, an appreciation of this process is necessary to estimate the risk-to-benefit ratio of a drug and to realize the limitations of the data that support the efficacy and safety of a marketed product.

By the time an IND application has been initiated and a drug reaches the stage of testing in human beings, its pharmacokinetic, pharmacodynamic, and toxic properties have been evaluated *in vitro* and in several species of animals in accordance with regulations and guidelines published by the FDA. Although the value of many requirements for preclinical testing is self-evident, such as those that screen for direct toxicity to organs and characterize dose-related effects, the value of others is controversial, particularly because of the well-known interspecies variation in the effects of drugs. Interestingly, although many of the preclinical tests have not been convincingly shown to predict effects that are eventually observed in human beings, the risk of cautious testing of a new drug is surprisingly low.

Trials of drugs in human beings in the United States are generally conducted in three phases that must be completed before an NDA can be submitted to the FDA for review; these are outlined in Figure 3-5. Although assessment of risk is a major objective of such testing, this is far more difficult than is the determination of whether or not a drug is efficacious for a selected clinical condition. Usually about 500 to 3000 carefully selected patients receive a new drug during phase 3 clinical trials. At most, only a few hundred are treated for more than 3 to 6 months, regardless of the likely duration of therapy that will be required in practice. Thus, the most profound and overt risks that occur almost immediately after the drug is given can be detected in a phase 3 study, if these occur more often than once per 100 administrations. Risks that are medically important but delayed or less frequent than 1 in 1000 administrations may not be revealed prior to marketing. It is thus obvious that a number of unanticipated adverse and beneficial effects of drugs are detectable only after the drug is used broadly. The same can be more convincingly stated about most of the effects of drugs on children or the fetus, where premarketing experimental studies are restricted. It is for these reasons that many countries, including the United States, have established systematic methods for the surveillance of the effects of drugs after they have been approved for distribution (McDevitt and MacDonald, 1991; Kessler, 1993; *see also below*).

## ADVERSE DRUG REACTIONS AND DRUG TOXICITY

Any drug, no matter how trivial its therapeutic actions, has the potential to do harm. Adverse reactions are a cost of modern medical therapy. Although the mandate of the FDA is to ensure that drugs are safe and effective, both of these terms are relative. The anticipated benefit from any therapeutic decision must be balanced by the potential risks. Pa-

tients, to a greater extent than physicians, are unaware of the limitations of the premarketing phase of drug development in defining even relatively common risks of new drugs. Since only a few thousand patients are exposed to experimental drugs in more or less controlled and well-defined circumstances during drug development, adverse drug effects that occur as frequently as 1 in 1000 patients may not be detected prior to marketing. Postmarketing surveillance of drug usage is thus imperative to detect infrequent but significant adverse effects.

"Mechanism-based" adverse drug reactions (extensions of the principal pharmacological action of the drug) are relatively easily predicted by preclinical and clinical pharmacology studies. For "idiosyncratic" adverse reactions, which result from an interaction of the drug with unique host factors that are unrelated to the principal action of the drug, current approaches to "safety assessment," both preclinically and in clinical trials, are problematic. The relative rarity of severe idiosyncratic reactions (*e.g.*, severe dermatologic, hematologic or hepatologic toxicities) presents epidemiologic ascertainment issues. In addition, it is clear that a population risk of 1/1000 is not distributed evenly across the population; some patients, because of unique genetic or environmental factors, are at an extremely high risk, while the remainder of the population may be at low or no risk. In contrast to the human heterogeneity underlying idiosyncratic risk, the standard process of drug development, particularly the preclinical safety assessment using inbred healthy animals maintained in a defined environment on a defined diet and manifesting predictable habits, limits the identification of risk for idiosyncratic adverse drug reactions in the human population. Understanding the genetic and environmental bases of idiosyncratic adverse events holds the promise of assessing individual rather than population risk, thereby improving the overall safety of pharmacotherapy.

**Postmarketing Detection of Adverse Reactions.** Several strategies exist to detect adverse reactions after marketing of a drug, but debate continues about the most efficient and effective method. Formal approaches for estimation of the magnitude of an adverse drug effect are the follow-up or "cohort" study of patients who are receiving a particular drug and the "case-control" study, where the potential for a drug to cause a particular disease is assessed. Cohort studies can estimate the incidence of an adverse reaction, but they cannot, for practical reasons, discover rare events. To have any significant advantage over the premarketing studies, a cohort study must follow at least 10,000 patients who are receiving the drug to detect with 95% confidence one event that occurs at a rate

of 1 in 3300, and the event can be attributed to the drug only if it does not occur spontaneously in the control population. If the adverse event occurs spontaneously in the control population, substantially more patients and controls must be followed to establish the drug as the cause of the event (Strom and Tugwell, 1990). Case-control studies, on the other hand, can discover rare drug-induced events. However, it may be difficult to establish the appropriate control group (Feinstein and Horwitz, 1988), and a case-control study cannot establish the incidence of an adverse drug effect. Furthermore, the suspicion of a drug as a causative factor in a disease must be the impetus for the initiation of such case-control studies.

The magnitude of the problem of adverse reactions to marketed drugs is difficult to quantify. It has been estimated that 3 to 5% of all hospitalizations can be attributed to adverse drug reactions, resulting in 300,000 hospitalizations annually in the United States. Once hospitalized, patients have about a 30% chance of an untoward event related to drug therapy, and the risk attributable to each course of drug therapy is about 5%. The chance of a life-threatening drug reaction is about 3% per patient in the hospital and about 0.4% per each course of therapy (Jick, 1984). Adverse reactions to drugs are the most common cause of iatrogenic disease (Leape *et al.*, 1991).

Because of the shortcomings of both cohort and case-control studies, other approaches must be used. Spontaneous reporting of adverse reactions has proven to be an effective way to generate an early signal that a drug may be causing an adverse event. It is the only practical way to detect rare events, events that occur after prolonged use of drug, adverse effects that are delayed in appearance, and many drug-drug interactions. In the past few years, considerable effort has gone into improving the reporting system in the United States, which is now called MEDWatch (Kessler, 1993). Still, the voluntary reporting system in the United States is deficient when compared to the legally mandated systems of the United Kingdom, Canada, New Zealand, Denmark, and Sweden (Rogers *et al.*, 1988). Most physicians feel that detecting adverse reactions is a professional obligation, but relatively few actually report such reactions. Many physicians are not aware that the FDA has a reporting system for adverse drug reactions, even though the system has been repeatedly publicized in major medical journals.

The most important spontaneous reports are those that describe serious reactions, whether they have been described previously or not. Reports on newly marketed drugs (within the past three years) are the most significant, even though the physician may not be able to attribute a causal role to a particular drug. The major use of this sys-

tem is to provide early warning signals of unexpected adverse effects that can then be investigated by more formal techniques. However, the system also serves to monitor changes in the nature or frequency of adverse drug reactions due to aging of the population, changes in the disease itself, or the introduction of new, concurrent therapies. The primary sources for the reports are responsible, alert physicians; other potentially useful sources are nurses, pharmacists, and students in these disciplines. In addition, hospital-based pharmacy and therapeutics committees and quality assurance committees frequently are charged with monitoring adverse drug reactions in hospitalized patients, and reports from these committees should be forwarded to the FDA. The simple forms for reporting are now readily available in the *Physicians' Desk Reference* and *AMA Drug Evaluations* and are mailed to all physicians at least yearly as part of the *FDA Drug Bulletin*. Forms also may be obtained 24 hours a day, 7 days a week by calling (800)-FDA-1088 (Kessler, 1993). Additionally, health professionals may contact the pharmaceutical manufacturer, who is legally obligated to file reports with the FDA.

### GUIDE TO THE "THERAPEUTIC JUNGLE"

The flood of new drugs in recent years has provided many dramatic improvements in therapy, but it also has created a number of problems of equal magnitude. Not the least of these is the "therapeutic jungle," the term used to refer to the combination of the overwhelming number of drugs, the confusion over nomenclature, and the associated uncertainty of the status of many of these drugs. A reduction in the marketing of close congeners and drug mixtures and an improvement in the quality of advertising are important ingredients in the remedy for the "therapeutic jungle." However, physicians also can contribute to the remedy by employing nonproprietary rather than proprietary names whenever appropriate, by using prototypes both as an instructional device and in clinical practice, by adopting a properly critical attitude toward new drugs, and by knowing and making use of reliable sources of pharmacological information. Most important, they should develop a "way of thinking about drugs" based upon pharmacological principles.

**Drug Nomenclature.** The existence of many names for each drug, even when the names are reduced to a minimum, has led to a lamentable and confusing situation in drug nomenclature. In addition to its formal *chemical* name, a new drug is usually assigned a *code* name by the pharmaceutical manufacturer. If the drug appears promis-

ing and the manufacturer wishes to place it on the market, a *United States Adopted Name* (USAN) is selected by the USAN Council, which is jointly sponsored by the American Medical Association, the American Pharmaceutical Association, and the United States Pharmacopeial Convention, Inc. This *nonproprietary* name often is referred to as the *generic* name. This term has become entrenched, but by definition it more properly should be reserved to designate a chemical or pharmacological class of drugs, such as sulfonamides or sympathomimetics. If the drug is eventually admitted to *The United States Pharmacopeia* (see below), the USAN becomes the *official* name. However, the nonproprietary name and the official name of an older drug may differ. Subsequently, the drug also will be assigned a *proprietary* name or *trademark* by the manufacturer. If the drug is marketed by more than one company, it may have several proprietary names. If mixtures of the drug with other agents are marketed, each such mixture may also have a separate proprietary name.

There is increasing worldwide adoption of the same name for each therapeutic substance. For newer drugs, the USAN is usually adopted for the nonproprietary name in other countries, but this is not true for older drugs. International agreement on drug names is mediated through the World Health Organization and the pertinent health agencies of the cooperating countries.

One area of continued confusion and ambiguity is the designation of the stereochemical composition in the name of a drug. The nonproprietary names usually give no indication of the drug's stereochemistry, except for a few drugs such as levodopa and dextroamphetamine. Even the chemical names cited by the USAN Council often are ambiguous. Physicians and other medical scientists are frequently ignorant about drug stereoisomerism and are likely to remain so until the system of nonproprietary nomenclature incorporates stereoisomeric information (Gal, 1988).

The nonproprietary or official name of a drug should be used whenever possible, and such a practice has been adopted in this textbook. The use of the nonproprietary name is clearly less confusing when the drug is available under multiple proprietary names and when the nonproprietary name more readily identifies the drug with its pharmacological class. The best argument for the proprietary name is that it is frequently more easily pronounced and remembered as a result of advertising. **For purposes of identification, representative proprietary names, designated by SMALLCAP TYPE, appear throughout the text as well as in the index.** Not all proprietary names for drugs are included, because the number of proprietary names for a single drug may be large and because proprietary names differ from country to country.

The Drug Price Competition and Patent Term Restoration Act of 1984 allows more generic versions of brand name drugs to be approved for marketing. When the physician prescribes drugs, the question arises as to whether the nonproprietary name or a proprietary name should be employed. A pharmacist may substitute a preparation that is equivalent unless the physician indicates "no substitution" or specifies the manufacturer on the prescription. In view of the discussion above on the individualization of drug therapy, it is understandable why a physician who has carefully adjusted the dose of a drug to a patient's individual requirements for chronic therapy may be reluctant to surrender control over the source of the drug that the patient receives (Strom, 1987).

Based on a number of considerations, such as the frequency of use of a drug that is only available from a single manufacturer, the cost of filling a prescription, and the mark-up of the pharmacist, it appears as though the overall savings to society of prescribing the least expensive nonproprietary preparation is about 5% (see Trout and Lee, 1981). Of course, savings in individual situations can be very much greater. On the other hand, the lower wholesale cost of the nonproprietary preparation sometimes is not passed on to the consumer (Bloom *et al.*, 1986). More importantly, prescribing by nonproprietary name could result in the patient receiving a preparation of inferior quality or of uncertain bioavailability, and therapeutic failures due to decreased bioavailability have been reported (Hendeles *et al.*, 1993). To address this issue, the FDA has established standards for bioavailability and compiled information about the interchangeability of drug products, which is published annually (*Approved Drug Products with Therapeutic Equivalence Evaluations*). Because of potential cost savings to the individual patient and simplification of the "therapeutic jungle," nonproprietary names should be used when prescribing, except for drugs with a low therapeutic index and known differences in bioavailability among marketed products (Hendeles *et al.*, 1993).

**Use of Prototypes.** It is obviously crucial for the physician to be thoroughly familiar with the pharmacological properties of a drug before it is administered. It follows that the patient will benefit if the physician avoids the temptation to choose from many different drugs for the patient's regimen. A physician's needs for therapeutic agents usually can be satisfied by thorough knowledge of one or two drugs in each therapeutic category. Inevitably, a small number of drugs can be used more effectively. When the clinical setting calls for a drug that the physician uses infrequently, he or she should feel obligated to learn about its effects, to use great caution in its admin-

istration, and to apply appropriate procedures in monitoring its effects.

For teaching purposes in this textbook, the confusion created by the welter of similar drugs is reduced by restricting major attention to prototypes in each pharmacological class. A teaching prototype is often the agent most likely to be employed in clinical use, but this is not always true. A particular drug may be retained as the prototype, even though a new congener is clinically superior, either because more is known about the older drug or because it is more illustrative for the entire class of agents.

**Attitude Toward New Drugs.** A reasonable attitude toward new drugs is summarized by the adage that advises the physician to be "neither the first to use a new drug nor the last to discard the old." Only a minor fraction of new drugs represents a significant therapeutic advance. The limitation of information about toxicity and efficacy at the time of release of a drug has been emphasized above, and this is particularly pertinent to comparisons with older agents in the same therapeutic class. Nevertheless, the important advances in therapeutics in the last 50 years emphasize the obligation to keep abreast of significant advances in pharmacotherapy.

## SOURCES OF DRUG INFORMATION

The physician's need for objective, concise, and well-organized information on drugs is obvious. Among the available sources are textbooks of pharmacology and therapeutics, leading medical journals, drug compendia, professional seminars and meetings, and advertising. Despite this cornucopia of information, responsible medical spokespeople insist that most practicing physicians are unable to extract the objective and unbiased data required for the practice of rational therapeutics (Woosley, 1994).

Depending on their aim and scope, pharmacology textbooks provide (in varying proportions) basic pharmacological principles, critical appraisal of useful categories of therapeutic agents, and detailed descriptions of individual drugs or prototypes that serve as standards of reference for assessing new drugs. In addition, pharmacodynamics and pathological physiology are correlated. Therapeutics is considered in virtually all textbooks of medicine, but often superficially.

The source of information described as most often used by physicians in an industry survey is the *Physicians' Desk Reference* (PDR). The brand-name manufacturers whose products appear support this book. No comparative

data on efficacy, safety, or cost are included. The information is identical to that contained in drug package inserts, which are largely based on the results of phase 3 testing; its primary value is thus in learning what indications for use of a drug have been approved by the FDA.

There are, however, several inexpensive, unbiased sources of information on the clinical uses of drugs that are preferable to the industry-supported PDR. All recognize that the physician's legitimate use of a drug in a particular patient is not limited by FDA-approved labeling in the package insert. *The United States Pharmacopeia Dispensing Information* (USPDI), first published in 1980, comes in two volumes. One, *Drug Information for the Health Care Professional*, consists of drug monographs that contain practical, clinically significant information aimed at minimizing the risks and enhancing the benefits of drugs. Monographs are developed by USP staff and are reviewed by advisory panels and other reviewers. The *Advice for the Patient* volume is intended to reinforce, in lay language, the oral consultation provided by the therapist, and this may be provided to the patient in written form. These volumes are published frequently. *AMA Drug Evaluations*, compiled by the American Medical Association Department of Drugs in cooperation with the American Society for Clinical Pharmacology and Therapeutics, includes general information on the use of drugs in special settings (e.g., pediatrics, geriatrics, renal insufficiency, etc.) and reflects the consensus of a panel on the effective clinical use of therapeutic agents. *Facts and Comparisons* also is organized by pharmacological classes and is updated monthly. Information in monographs is presented in a standard format and incorporates FDA-approved information, which is supplemented with current data obtained from the biomedical literature. A useful feature is the comprehensive list of preparations with a "Cost Index," an index of the average wholesale price for equivalent quantities of similar or identical drugs. Many of these publications are available on diskette or CD-ROM for personal computers.

Industry promotion, in the form of direct-mail brochures, journal advertising, displays, professional courtesies, or the detail person or pharmaceutical representative, is intended to be persuasive rather than educational. The pharmaceutical industry cannot, should not, and indeed does not purport to be responsible for the education of physicians in the use of drugs.

Over 1500 medical journals are published regularly in the United States. However, of the two to three dozen medical publications with circulations in excess of 70,000 copies, the great majority are sent to physicians free of charge and paid for by the industry. In addition, special

supplements of some peer-reviewed journals are entirely supported by a single drug manufacturer whose product is prominently featured and favorably described. Objective journals, which are not supported by drug manufacturers, include *Clinical Pharmacology and Therapeutics*, which is devoted to original articles that evaluate the actions and effects of drugs in human beings, and *Drugs*, which publishes timely reviews of individual drugs and drug classes. The *New England Journal of Medicine*, *Annals of Internal Medicine*, *Journal of the American Medical Association*, *Archives of Internal Medicine*, *British Medical Journal*, *Lancet*, and *Postgraduate Medicine* offer timely therapeutic

reports and reviews. *The Medical Letter* provides objective summaries, in a biweekly newsletter, of scientific reports and consultants' evaluations of the safety, efficacy, and rationale for use of a drug.

*The United States Pharmacopeia* (USP) and *The National Formulary* (NF) were recognized as "official compendia" by the Federal Food and Drug Act of 1906. The approved therapeutic agents used in medical practice in the United States are described and defined with respect to source, chemistry, physical properties, tests for identity and purity, assay, and storage. The two official compendia are now published in a single volume.

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# EXHIBIT 43

# From Idea to Market: The Drug Approval Process

*Martin S. Lipsky, MD, and Lisa K. Sharp, PhD*

**Background:** Each year many new prescription drugs are approved by the Food and Drug Administration (FDA). The process of developing and bringing new drugs to market is important for primary care physicians to understand.

**Methods:** We describe the drug development process based on a review of the literature and Web sites addressing FDA processes and policies.

**Results:** The process starts with preclinical testing. For drugs that appear safe, an investigational new drug application is filed with the FDA. If approved, clinical trials begin with phase 1 studies that focus on safety and pharmacology. Phase 2 studies examine the effectiveness of the compound. Phase 3 is the final step before submitting a new drug application (NDA) to the FDA. An NDA contains all the information obtained during all phases of testing. Phase 4 studies, or postmarketing studies, are conducted after a product is approved. Recent changes in legislation have streamlined the approval process. Critics contend that these changes have compromised public safety, resulting in the need to recall several products from the market. Proponents claim that changes in the approval process help patients with debilitating diseases, such as acquired immunodeficiency syndrome, that were previously denied critical medication because of bureaucratic regulations. (J Am Board Fam Pract 2001;14:362–7.)

The Food and Drug Administration (FDA) is responsible for assuring that foods and cosmetics are safe and that medicines and medical devices are both safe and effective. To carry out this responsibility, the FDA monitors more than \$1 trillion worth of products, representing about \$0.25 of every \$1.00 spent annually by American consumers.<sup>1</sup> Balancing the efficacy and safety of these products is the core public health protection duty of the FDA. This mission requires examining efficacy as determined from well-controlled trials, effectiveness as determined from actual use in uncontrolled settings, and safety for both prescription and over-the-counter pharmaceuticals before approving a medication for market. During the past decade alone, more than 500 new prescription drugs have been approved by the FDA.

Physicians face the continual challenge of learning about new products approved by the FDA. The process of developing new drugs and bringing new drugs to market has important practice implications yet is poorly understood by most primary care physicians. Understanding how clinical trials are conducted is important when physicians consider

the use of a new medication for patients in their own practices. For example, the medical literature or a pharmaceutical representative might refer to a phase 3 or phase 4 study. Table 1 provides a brief description of these terms and others used throughout this article. Understanding these terms will help the physician understand the risks involved in using a new medicine and the role of clinical trials in evaluating safety and effectiveness. Primary care physicians who might receive invitations to participate in clinical trials need to understand the risks involved for patients and the importance such investigations play in determining efficacy and safety issues of newly released medications. Finally, physicians who challenge the cost of new medications might benefit from a more complete understanding of the time, cost, and complex issues involved in having a new product approved by the FDA.

The purpose of this article is to present a concise overview of the drug approval process. It will briefly review the history of the FDA and follow the journey of a new product from early development until approval by the FDA for prescription use.

## Methods

We describe the drug development process based on a review of the literature and Web sites addressing FDA processes and policies. Key words used for the searches included “Food and Drug Administra-

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**Table 1. Terms and Definitions Relating to the New Drug Development Process.**

Term	Definition
Clinical evaluation, phase 1	Examines the pharmacologic actions and safe dosage range of a drug; how it is absorbed, distributed, metabolized, and excreted; and its duration of action
Clinical evaluation, phase 2	Controlled studies in volunteers to assess the effectiveness of a drug. Simultaneous animal and human studies can continue to examine further the safety of the drug
Clinical evaluation, phase 3	Testing using a greater number of volunteer patients. The drug is administered by practicing physicians to those suffering from the condition the drug is intended to treat. These studies must confirm earlier efficacy studies and determine low-incidence adverse reactions
Clinical evaluation, phase 4	Studies conducted after FDA approval, during general use of the drug by medical practitioners. Also referred to as postmarketing studies
Fast-track drugs	Fast-track approval provided for drugs that meet unmet medical needs for patients with serious or life-threatening conditions
Labeling	Any information distributed about a drug by the manufacturer, even if it is not physically affixed to the product. In addition to package inserts, labeling includes such material as advertising
Misbranding	Anything in labeling that is “false or misleading in any particular” renders the product misbranded, making it subject to FDA regulatory action

FDA - Food and Drug Administration.

tion,” “drug development,” and “drug approval.” The databases searched were MEDLINE and CINAHL. Also, Web sites were sought using the Lycos search engine, and “Food and Drug Administration” and “drug approval” as key words.

### **FDA: A Historical Perspective**

Misfortune, disaster, and tragedy have triggered most of the advances in drug regulation. At the turn of the 19th century, the marketing of medicines was not controlled, and corruption, exploitation, and fraud were rampant. Public disclosures about the unsanitary conditions in meat-packing plants and concerns about worthless or even dangerous medicines led to the enactment of the Food and Drug Administration Act of 1906. This law (1) required that drugs meet official standards of strength and purity, (2) defined the terms *adulterated* and *misbranded*, and (3) prohibited the shipment for sale of misbranded and adulterated foods, drinks, and drugs.<sup>2-4</sup>

The FDA gained little power from this legislation, and it did not prevent the accidental deaths of 107 persons in 1937 from the patent medicine mar-

keted as “elixir sulfanilamide.” A well-intentioned chemist used diethylene glycol as a solvent to make a liquid formulation of sulfanilamide that would be easier for children to take. Although the toxicity of diethylene glycol was known at the time, the manufacturer was not aware of it.<sup>5</sup> Existing law did not require that manufacturers demonstrate a drug’s safety, and 240 gallons of the elixir were released into the marketplace.

As a consequence of this event, Congress enacted the Federal Food, Drug and Cosmetic Act of 1938, marking the birth of the modern FDA. The new act required that a manufacturer (not the FDA) prove the safety of a drug before it could be marketed, authorized factory inspections, and established penalties for fraudulent claims and misleading labels. Following the 1938 Act, the FDA began to distribute public notices (known as trade correspondences) to the industry regarding the labeling and dispensing of drugs. It was in these public notices that the FDA first distinguished medications that should be available only by prescription.<sup>3</sup> Specifically it required that all drugs either carry a label with adequate information for

consumer use or a caution label. The caution label warned consumers that the drug should be used only by or on prescription of a physician.

At this point the decision about which drugs should receive a caution label was largely at the discretion of the manufacturer. In 1951, the Durham-Humphrey Amendment set forth the basis for distinguishing between prescription and nonprescription drugs. The amendment specified that three classes of drug be available by prescription: habit-forming drugs, drugs considered unsafe for use except under expert supervision because of toxicity or other potential harmful effects, and drugs limited to prescription use only under a manufacturer's new drug application.<sup>4</sup>

In 1961, an Australian obstetrician, William McBride, reported an increase of fetal malformations in association with the hypnotic drug thalidomide. Although thalidomide was heavily marketed in Western Europe, approval of this drug was delayed by the FDA in the United States and never made it to market. This near catastrophe, however, highlighted the need for more stringent laws, and in 1962, Congress passed the Kefauver-Harris Amendment. This act not only required that manufacturers prove to the FDA that a drug is safe but, for the first time, required that the manufacturer provide evidence that the product was effective for the claims made in labeling.<sup>6</sup> Effectiveness needed to be established through adequate and well-controlled investigations by qualified researchers.

In the late 1970s there was concern about the quality of scientific data submitted to the FDA. This concern led to the establishment of good laboratory practices and guidelines for clinical trials to assure the quality and integrity of the safety data filed with the FDA. Important elements of the guidelines included the qualifications of the investigator, the study facilities, study management, safeguards for the safety and rights of patients, adherence to the research protocol, record keeping, and study monitoring. Many of these guidelines have now become regulation, such as the need to provide informed consent and the basic elements of informed consent, and essentially spell out the requirements for institutional review boards (IRBs).<sup>7</sup>

In 1987, partially in response to the human immunodeficiency virus (HIV) epidemic, new regulations were developed to accelerate approval for high-priority medications. Before then, drugs were approved based on their effect on the illness or on

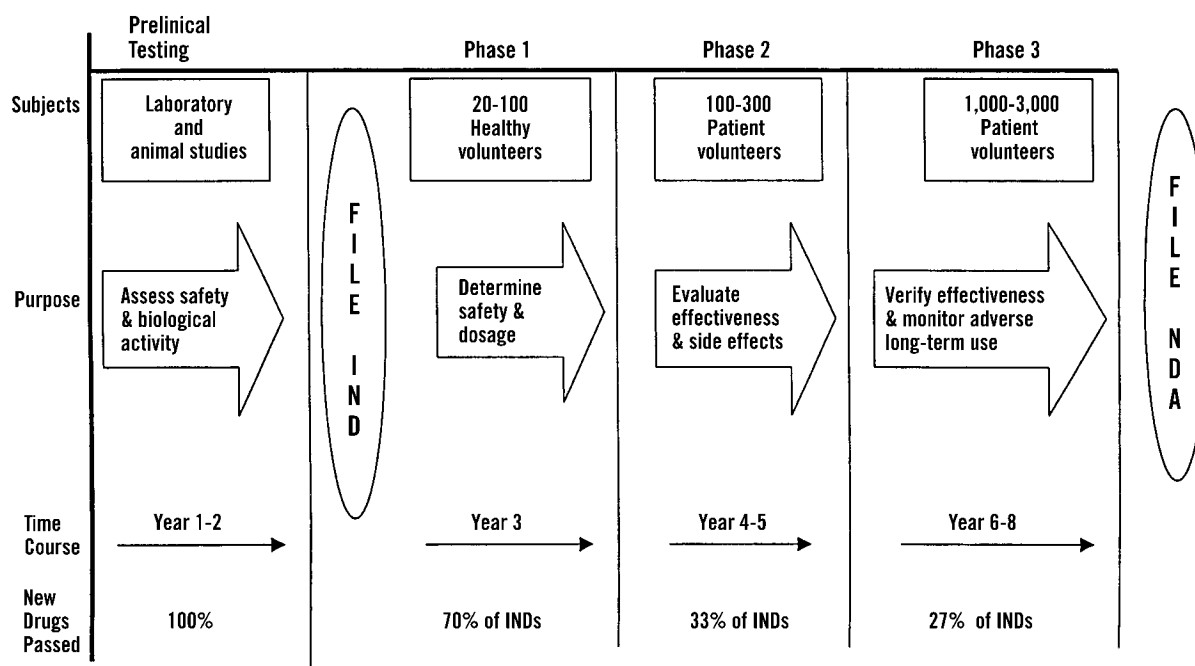
survival. Accelerated approval allowed the FDA to judge drugs using a surrogate endpoint, or the effect of the drug on a physiologic process or marker associated with a disease. For example, CD4 cell counts could be used to measure the effectiveness of an antiviral medication in treating HIV-infected patients. This new standard allowed the FDA to approve a promising drug without completing a full clinical trial.<sup>6</sup>

## Drug Development

Drug development can generally be divided into phases. The first is the preclinical phase, which usually takes 3 to 4 years to complete. If successful, this phase is followed by an application to the FDA as an investigational new drug (IND). After an IND is approved, the next steps are clinical phases 1, 2, and 3, which require approximately 1, 2, and 3 years, respectively, for completion (Table 1). Importantly, throughout this process the FDA and investigators leading the trials communicate with each other so that such issues as safety are monitored. The manufacturer then files a new drug application (NDA) with the FDA for approval. This application can either be approved or rejected, or the FDA might request further study before making a decision. Following acceptance, the FDA can also request that the manufacturer conduct additional postmarketing studies. Overall, this entire process, on average, takes between 8 to 12 years.<sup>2</sup> Figure 1 summarizes the drug approval process.

It is not surprising that from conception to market most compounds face an uphill battle to become an approved drug. For approximately every 5,000 to 10,000 compounds that enter preclinical testing, only one is approved for marketing.<sup>8</sup> A 1993 report by the Congressional Office of Technology Assessment estimated the cost of developing a new drug to be \$359 million.<sup>9</sup> Newer figures place the cost at more than \$500 million.<sup>10</sup>

The first step, a preclinical phase, is to find a promising agent, which involves taking advantage of the advances made in understanding a disease, pharmacology, computer science, and chemistry. Breaking down a disease process into its components can provide clues for targeting drug development. For example, if an enzyme is determined to be a key component of a disease process, a researcher might seek ways to inhibit this enzyme.



**Figure 1. Overview of drug development process and review. IND - investigational new drug, NDA - new drug application. Adapted from: The Drug Development Approval Process. Available at <http://www.phrma.org/charts/approval.html>.**

Advances in basic science might help by ascertaining the active enzyme site. Numerous compounds might be synthesized and tested before a promising agent emerges. Computer modeling often helps select what compounds might be the most promising.

The next step before attempting a clinical trial in humans is to test the drug in living animals, usually rodents. The FDA requires that certain animal tests be conducted before humans are exposed to a new molecular entity. The objectives of early in vivo testing are to demonstrate the safety of the proposed medication. For example, tests should prove that the compound does not cause chromosomal damage and is not toxic at the doses that would most likely be effective. The results of these tests are used to support the IND application that is filed with the FDA. The IND application includes chemical and manufacturing data, animal test results, including pharmacology and safety data, the rationale for testing a new compound in humans, strategies for protection of human volunteers, and a plan for clinical testing.<sup>2,9</sup> If the FDA is satisfied with the documentation, the stage is set for phase 1 clinical trials.

Phase 1 studies focus on the safety and pharmacology of a compound.<sup>11</sup> During this stage low

doses of a compound are administered to a small group of healthy volunteers who are closely supervised. In cases of severe or life-threatening illnesses, volunteers with the disease may be used. Generally, 20 to 100 volunteers are enrolled in a phase 1 trial. These studies usually start with very low doses, which are gradually increased. On average, about two thirds of phase 1 compounds will be found safe enough to progress to phase 2.

Phase 2 studies examine the effectiveness of a compound. To avoid unnecessarily exposing a human volunteer to a potentially harmful substance, studies are based on an analysis of the fewest volunteers needed to provide sufficient statistical power to determine efficacy. Typically, phase 2 studies involve 100 to 300 patients who suffer from the condition the new drug is intended to treat. During phase 2 studies, researchers seek to determine the effective dose, the method of delivery (eg, oral or intravenous), and the dosing interval, as well as to reconfirm product safety.<sup>2,7,11,12</sup> Patients in this stage are monitored carefully and assessed continuously. A substantial number of these drug trials are discontinued during phase 2 studies. Some drugs turn out to be ineffective, while others have safety problems or intolerable side effects.

Phase 3 trials are the final step before seeking FDA approval. During phase 3, researchers try to confirm previous findings in a larger population. These studies usually last from 2 to 10 years and involve thousands of patients across multiple sites. These studies are used to demonstrate further safety and effectiveness and to determine the best dosage. Despite the intense scrutiny a product receives before undergoing expensive and extensive phase 3 testing, approximately 10% of medications fail in phase 3 trials.

If a drug survives the clinical trials, an NDA is submitted to the FDA. An NDA contains all the preclinical and clinical information obtained during the testing phase. The application contains information on the chemical makeup and manufacturing process, pharmacology and toxicity of the compound, human pharmacokinetics, results of the clinical trials, and proposed labeling. An NDA can include experience with the medication from outside the United States as well as external studies related to the drug.

After receiving an NDA, the FDA completes an independent review and makes its recommendations. The Prescription Drug User Fee Act of 1992 (PDUFA) was designed to help shorten the review time. This act allowed the agency to collect user fees from pharmaceutical companies as financial support to enhance the review process. The 1992 act specifies that the FDA reviews a standard drug application within 12 months and a priority application within 6 months. Application for drugs similar to those on the market are considered standard, whereas priority applications represent drugs offering important advances in addition to existing treatments. If during the review the FDA staff feels there is a need for additional information or corrections, they will make a written request to the applicant. During the review process it is not unusual for the FDA to interact with the applicant staff.<sup>12</sup>

Once the review is complete, the NDA might be approved or rejected. If the drug is not approved, the applicant is given the reasons why and what information could be provided to make the application acceptable. Sometimes the FDA makes a tentative approval recommendation, requesting that a minor deficiency or labeling issue be corrected before final approval. Once a drug is approved, it can be marketed.

Some approvals contain conditions that must be met after initial marketing, such as conducting additional clinical studies. For example, the FDA might request a postmarketing, or phase 4, study to examine the risks and benefits of the new drug in a different population or to conduct special monitoring in a high-risk population. Alternatively, a phase 4 study might be initiated by the sponsor to assess such issues as the longer term effects of drug exposure, to optimize the dose for marketing, to evaluate the effects in pediatric patients, or to examine the effectiveness of the drug for additional indications.<sup>7</sup> Postmarketing surveillance is important, because even the most well-designed phase 3 studies might not uncover every problem that could become apparent once a product is widely used. Furthermore, the new product might be more widely used by groups that might not have been well studied in the clinical trials, such as elderly patients. A crucial element in this process is that physicians report any untoward complications. The FDA has set up a medical reporting program called Medwatch to track serious adverse events (1-800-FDA-1088). The manufacturer must report adverse drug reactions at quarterly intervals for the first 3 years after approval,<sup>10</sup> including a special report for any serious and unexpected adverse reactions.

### **Recent Developments in Drug Approval**

The Food and Drug Administration Modernization Act of 1997 (FDAMA) extended the use of user fees and focused on streamlining the drug approval process.<sup>11,13</sup> In 1999, the 35 drugs approved by the FDA were reviewed in an average of 12.6 months, slightly more than the 12-month goal set by PDUFA.<sup>10</sup> This act also increased patient access to experimental drugs and facilitated an accelerated review of important new medications. The law ended the ban on disseminating information to providers about non-FDA-approved uses of medications. A manufacturer can now provide peer-reviewed journal articles about an off-label indication of a product if the company commits to filing a supplemental application to establish the use of the unapproved indication. As part of this process, the company must still conduct its own phase 4 study. As a condition for an accelerated approval, the FDA can require the sponsor to carry out postmarketing studies to confirm a clinical benefit and product safety.

Critics contend the 1997 act compromises public safety by lowering the standard of approval.<sup>14</sup> Within a year after the law was passed, several drugs were removed from the market. Among these medications were mibefradil for hypertension, dexfenfluramine for morbid obesity, the antihistamine terfenadine, and bromfenac sodium for pain.<sup>15</sup> More recently, additional drugs including troglitazone were removed from the market. Although the increase in recalls might reflect the dramatic increase in drugs approved and launched,<sup>15</sup> others argue that several safety questions were ignored.<sup>16,17</sup> Another concern was that many withdrawn drugs were me-too drugs which did not represent a noteworthy advance in therapy. Persons critical of the FDA believe changes in the approval process, such as allowing some new drugs to be approved based on only a single clinical trial, expanded use of accelerated approvals, and the use of surrogate end points, have created a dangerous situation.<sup>17</sup> Proponents of the changes in the approval process argue that there is no evidence of increased risk from the legislative changes,<sup>18</sup> and that these changes improve access to cancer patients and those with debilitating disease who were previously denied critical and lifesaving medications.

## Conclusion

New drugs are an important part of modern medicine. Just a few decades ago, a disease such as peptic ulcers was a frequent indication for major surgery. The advent of new pharmacologic treatments has dramatically reduced the serious complications of peptic ulcer disease. Likewise, thanks to many new antiviral medications, the outlook for HIV-infected patients has improved dramatically. It is important that physicians understand the process of approving these new medications. Understanding the process can promote innovation, help physicians assess new products, underline the importance of reporting adverse drug events, and provide physicians with the information to educate patients about participating in a clinical trial.

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